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RADIOPAQUE DIAGNOSTIC AGENTS*

Consulting Editor

MAXWELL H. POPPEL

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GENERAL ASPECTS OF CONTRAST MEDIA RESEARCH

Vernon H. Wallingford
Mallinckrodt Chemical Works, St. Louis, Mo.

In recent years we have become accustomed to "crash" programs, but we can still marvel at the alacrity with which physicians applied X rays in their work. In 1895, within 1 month after the announcement of the discovery of these penetrating radiations, patients were being examined by this means.[1] At the St. Louis University School of Medicine, St. Louis, Mo., there is on display crude X ray equipment that A. V. L. Brokaw constructed and used in his medical practice "about 1896." Doubtless similar mementos can be found in many medical centers.

An early experimenter in the medical uses of X rays in this country was W. B. Cannon of Harvard University, Cambridge, Mass. One of his early papers[2] gives an amusing picture of a goose with its neck enclosed in a device similar to a mailing tube to hold it motionless during observation by means of a fluorescent screen. To uncover the secrets of the esophagus and the process of swallowing, Cannon stuffed down the throat of the goose various foods mixed with bismuth subnitrate. In all probability bismuth subcarbonate or subnitrate were used in these and similar investigations, although powdered iron or lead shot were also popular media of early radiologists. Observation of the esophagus logically led to observation of the stomach and the complete gastrointestinal tract.

Gastrointestinal Media

The first gastrointestinal (G.I.) radiographs in humans were made using "bismuth meal" (either bismuth subcarbonate or subnitrate) as the opaque material, but this was displaced by barium sulfate as recommended by the German physicians Bachem and Günther[3] in 1910. At the request of Cannon, who was dissatisfied with the available barium sulfate, H. V. Farr* prepared a special form of barium sulfate by the addition of sulfuric acid to a suspension of barium carbonate. The resulting finely precipitated product proved superior and, in 1913, was introduced especially for X-ray diagnosis. During the intervening years much effort has been expended to improve the product and to lower costs. The uniqueness of barium sulfate as an X-ray medium is attested by the fact that it has not been superseded for gastrointestinal radiography in nearly 50 years.

Several prepared formulations based on barium sulfate are offered by commercial suppliers.† These contain suspending agents or flavors designed to increase their effectiveness for certain uses or to improve their palatability.

A barium sulfate of extremely small particle size, Micropaque,‡ is produced

---

* Of Mallinckrodt Chemical Works, St. Louis, Mo.

† Throughout this paper the familiar trade names are employed. The ownership of the registered trade names will be clear from the context and, in most cases, it will have been indicated—at least at first mention.

‡ Product of Damancy and Company, Ltd., Ware, England; distributed in the United States by the Picker X-Ray Corporation, White Plains, N. Y.

TABLE 1

MEDIA FOR GASTROINTESTINAL ROENTGENOGRAPHY

Barium sulfate U.S.P.	
Barium sulfate formulations	At least 17 of United States manufacture; at least 8 imported
Micropaque	Finely divided barium sulfate
Umbrathor	Colloidal thorium dioxide, 25 per cent w/v
Gastrografin	Flavored aqueous solution, 76 per cent w/v of N-methylglucamine salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid

in England. Colloidal thorium dioxide, 25 per cent, known as Umbrathor,* is also used for opacifying portions of the gastrointestinal tract, as well as in cystography.

A new approach to the X-ray examination of the G.I. tract is the use of the water-soluble organic iodine compounds (urographic agents), which will be more fully described later. These media are of low toxicity and are not significantly absorbed by the system after oral administration. In 1956, Davis *et al.*[4] reported excellent results using Urokon† and Hypaque‡. The low viscosity of these media permits detection of small lesions and narrow fistulas. Clinical trials with Gastrografin,§ a new medium for gastrointestinal roentgenography, were reported in July 1958 by Robinson and Levene[5] and by Jacobson *et al.*[6] TABLE 1 lists the G.I. radiopaque media available at the present time.

Oils and Suspensions

The iodinated oils and suspensions constitute a distinct class of opaque media. Currently used media of this type are listed in TABLE 2.

Iodinated poppy seed oil, or Lipiodol,‖ introduced in 1922, was the first organic iodine compound used as a contrast agent. It is supplied with 40, 28 and 10 per cent of iodine by weight and is used for radiographic visualization of a wide variety of tissues and organs. The iodinated oils are nonirritating, but are only slowly absorbed and eliminated by the tissues of the body. Directions for use frequently call for the withdrawal of the oil from the site of injection after it has served its purpose. The oily media, being bland, have been injected into almost every cavity or duct of the human body, and have played an important role in the development of radiography. Their usefulness and safety would be enhanced if they could be made more readily absorbable.

A 50 per cent emulsion of ethyl iodophenylundecylate¶ and an equivalent product** are available. These are comparatively new formulations and are used in cholangiography and a variety of other applications, as indicated in TABLE 2.

---

* Marketed by Testagar & Co., Inc., Detroit, Mich.

† Product of Mallinckrodt Chemical Works.

‡ Manufactured by Winthrop Laboratories, New York, N. Y.

§ A special formulation of the urographic medium Renografin, both products of E. R. Squibb & Sons, New York, N. Y.

‖ Product of E. Fougera & Co., Inc., New York, N. Y.

¶ Product of Lafayette Pharmacal, Inc., Lafayette, Ind.

** Mulsopaque, distributed by General Electric Co., New York, N. Y.

TABLE 2

OILS AND SUSPENSIONS

Trade name*	Composition	Recommended applications
Lipiodol Lafay 40% (Fougera)	Iodinated poppy seed oil containing 40% iodine	For visualization of a wide variety of tissues and organs, namely in the bronchopulmonary apparatus, genito-urinary tract, paranasal sinuses, fistula and sinus tracts, and in myelography
Lipiodol Lafay 28% (Fougera)	Iodinated poppy seed oil containing 28% iodine	Hollow viscera, sinus and fistula tracts
Lipiodol Lafay 10% (Fougera)	Iodinated poppy seed oil containing 10% iodine	Myelography
Iodochlorol (Searle)	Halogenated peanut oil, 27% iodine, and 7.5% chlorine	Hysterosalpingography, urethrography, bronchography, and visualization of sinuses, fistulas, empyema cavities, and biliary tract
Ethiodol (Fougera)	Ethyl esters of iodinated fatty acids of poppy seed oil, 37% iodine	Hysterosalpingography, sialography, visualization of sinuses and fistulous tracts
Pantopaque (Lafayette and Westinghouse Electric)	Ethyl iodophenylundecylate	Myelography
50% Emulsion ethyl iodophenylundecylate (Lafayette) Mulsopaque (General Electric)	50% Aqueous emulsion of ethyl iodophenylundecylate (Pantopaque)	Cholangiography, sinus tracts, fistulas, empyema cavities, ducts, breast and salivary glands
Visciodol (Fougera)	Suspension of sulfanilamide 32% w/v in Lipiodol 40%	Bronchography
Dionosil Aqueous (Glaxo and Picker X-Ray)	50% w/v Aqueous suspension of *n*-propyl 3,5-diiodo-4-pyridone-N-acetate	Bronchography
Dionosil Oily (Glaxo and Picker X-Ray)	Oily suspension of *n*-propyl 3,5-diiodo-4-pyridone-N-acetate	Bronchography
Thorotrast (Testagar)	25% w/v Sterile colloidal suspension of thorium dioxide	Arteriography, venography, cerebral angiography, lymphangiography, and hepatolienography

* Name in parentheses is of manufacturer, distributor, or both. Addresses of those not given in footnotes to the text are as follows: G. D. Searle & Co., Chicago, Ill., and Westinghouse Electric Corporation, Baltimore, Md.

In recent years new media have been introduced to supplement or even supplant the older oily media in some of their classic applications. Two suspensions of solid *n*-propyl-3,5-diiodo-4-pyridone-N-acetate (Dionosil)* are available: one in an aqueous, the other in an oily, menstruum. These media are used in bronchography. The iodine-containing moiety is stated to be completely absorbed and excreted by way of the urine within a few days. Thickened aqueous solutions of the water-soluble urographic media, described later,

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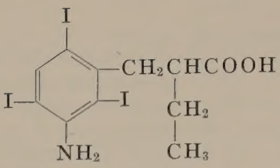
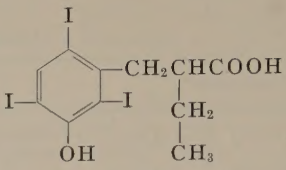
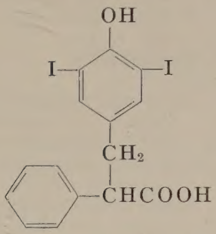
* Products of The Glaxo Laboratories Ltd., London, England; distributed in the United States by the Picker X-Ray Corporation.



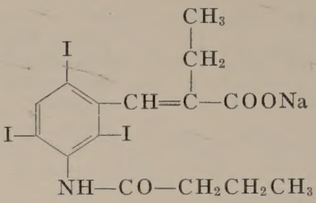
Telepaque (Winthrop)
3-(3-Amino-2,4,6-triiodophenyl)-2-ethylpropionic acid



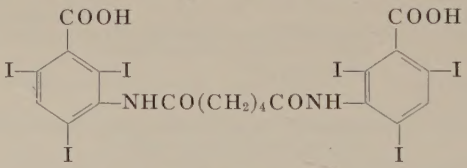
Teridax (Schering)
3-(3-Hydroxy-2,4,6-triiodophenyl)-2-ethylpropionic acid



Priodax (Schering)
Perfectochol (Lafayette)
3-(4-Hydroxy-3,5-diiodophenyl)-2-phenylpropionic acid



Orabilex (Fougera)
Sodium 3-(3-butyrylamino-2,4,6-triiodophenyl)-2-ethylacrylate



Cholografin (Squibb)
Methylglucamine or sodium salt of N,N′-adipyl-bis-(3-amino-2,4,6-triiodobenzoic acid)

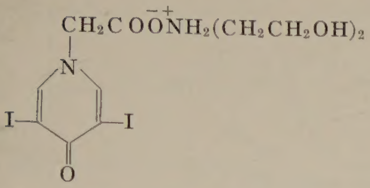
FIGURE 1. Cholecystographic contrast media. Teridax and Priodax are products of Schering Corporation, Bloomfield, N. J. Addresses of other manufacturers are given in text.

have invaded the field formerly held by the iodized oils, notably in hysterosalpingography and urethrography.

Cholecystographic Media

The advent of cholecystography in 1923 to 1924 was important in two ways to the general future of radiography. It was the first successful and practical application of an opaque medium by the intravenous route, and it was the first use of a natural physiological function to collect and concentrate a radiopaque material in the desired region of the body. The original conception was by the late Evarts A. Graham of the Washington University School of Medicine in St. Louis, Mo. Graham's idea was based on the known fact that certain substances are selectively excreted by the liver and concentrated in the bile. At his suggestion, a manufacturer* prepared tetraiodophenolphthalein and intro-

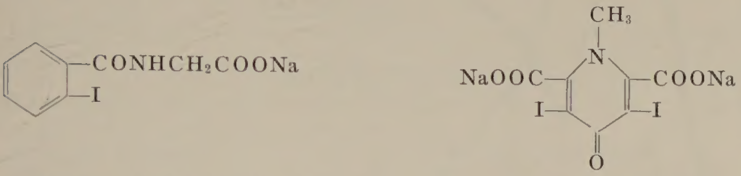
* Mallinckrodt Chemical Works.



ICH_2SO_3Na

Diodrast (Winthrop)
Diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid

Skiodan (Winthrop)
Sodium iodomethane sulfonate



Hippuran (Mallinckrodt)
Sodium *o*-iodohippurate

Neo-Iopax (Schering)
Disodium salt of N-methyl-3,5-diiodochelidamic acid

FIGURE 2. Earlier urographic media.

duced it in 1924 as Iodeikon. This compound was administered either intravenously or orally. I worked with Graham in an investigation of various organic iodine compounds for use in cholecystography; none proved superior to Iodeikon, which became the standard radiopaque medium for this purpose for more than twenty years.

The cholecystographic media used today are listed in FIGURE 1. These were developed over the last eighteen years and are the result of much excellent chemical and pharmacological work on the part of the various laboratories. Of the agents listed, Cholografin* is comparatively new and is the only agent recommended for intravenous injection. It is able to delineate the bile ducts (intravenous cholangiography) during the course of its excretion. Orabilex (Bunamiodyl),† a new medium for oral cholecystography and cholangiography was announced recently.

Urographic Media

Excretion by the kidneys is another physiological process utilized to transport and concentrate an opaque medium. In the earliest attempts at intravenous urography, sodium iodide was used, resulting in serious side effects. In 1929, Uroselectan, the sodium salt of 5-iodo-2-pyridone-N-acetic acid was introduced in Germany. This first organic urographic contrast medium was superseded by other urographic media that became available in the early thirties. Hippuran, sodium *o*-iodohippurate, was introduced by a manufacturer‡ in 1933 in cooperation with M. Swick, who had participated in the development of the original medium. The media shown in FIGURE 2 are part of the present armamentarium of the radiologist, and each has its particular field of application.

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* Manufactured by E. R. Squibb & Sons.
† Product of E. Fougera & Co., Inc.
‡ Mallinckrodt Chemical Works.

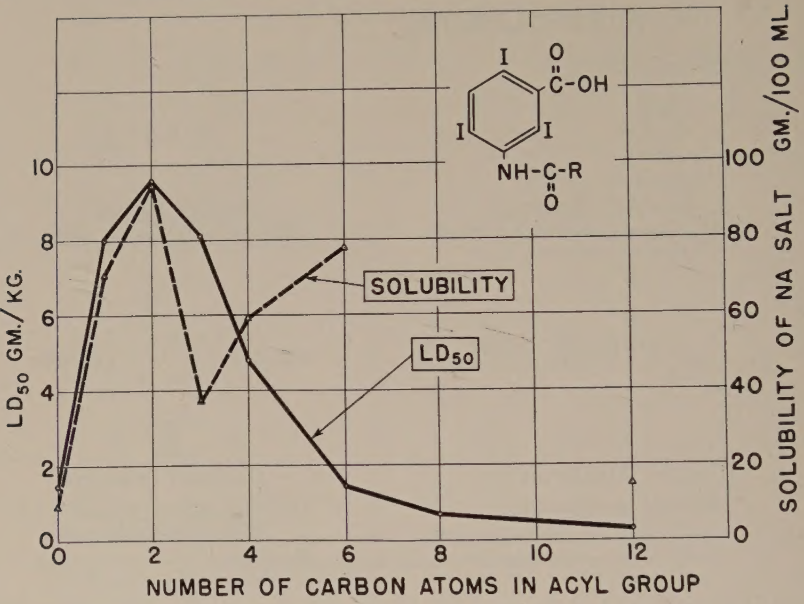

FIGURE 3. Properties of 3-acylamino-2,4,6-triiodobenzoic acids.

A notable advance in contrast media was made in 1951 with the development of Urokon,* the sodium salt of 3-acetamido-2,4,6-triiodobenzoic acid, a distinctly new type of contrast medium. FIGURE 3, taken from my paper of 1952,[7] shows the astonishing effect of varying the number of carbons in the acyl group. Maximum solubility and median lethal dose (LD_{50}) were attained when the acyl group contained 2 carbons (acetyl). The 3-acetylamino derivative (Urokon) is ten times as soluble and only one sixth as toxic as the parent amino compound; it became widely used as a urographic agent and proved useful in many other applications.

The examination of compounds closely related to Urokon has yielded several new and useful X-ray media, as shown in FIGURE 4. These are grouped to emphasize certain chemical similarities; all embody the triiodinated benzoic acid nucleus and contain acylamino groups characteristic of the original Urokon. The low toxicity of the new cholecystographic medium Orabilex, previously described, is attributed to the butyrylamino group, an important structural feature of that compound. With the exception of Cholografin, the media in FIGURE 4 are intravenous urographic forms, although they have many other uses. Cholografin is supplied either as the sodium salt or the methylglucamine salt and, as previously mentioned, is used intravenously for cholecystography and for delineating the bile ducts in intravenous cholangiography. To meet the requirements of various applications, most of the urographic media are supplied in more than 1 concentration or formulation. Retrografin† is 30

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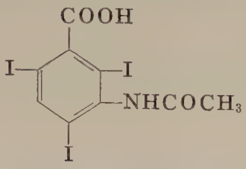
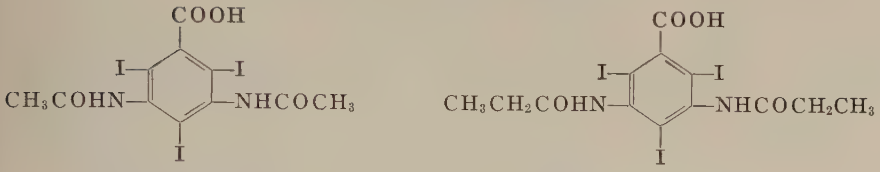
* Mallinckrodt Chemical Works.
† E. R. Squibb & Sons.



Urokon (Mallinckrodt)
3-Acetamido-2,4,6-triiodobenzoic acid

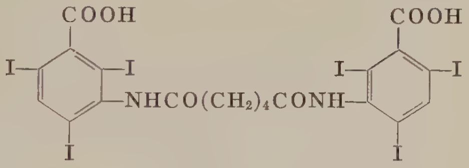


Hypaque (Winthrop)
Renografin (Squibb)

3,5-Bisacetamido-2,4,6-triiodobenzoic acid

Miokon (Mallinckrodt)

3,5-Bispropionylamino-2,4,6-triiodobenzoic acid



Cholografin (Squibb)

N,N′-Adipyl-bis-(3-amino-2,4,6-triiodobenzoic acid)

FIGURE 4. Urokon and chemically related contrast agents.

per cent Renografin and 2.5 per cent neomycin, and is used in retrograde pyelography, in the presence of frank or suspected genitourinary infection. A 20 per cent solution of sodium 3-acetamido-2,4,6-triiodobenzoate was recently released under the trade name Pyelokon-R* for retrograde use.

Several of the water-soluble media are available as viscous or thickened solutions. Their compositions and the techniques for which they are approved are listed in TABLE 3.

A thickened 50 per cent solution of Urokon was recently introduced under the name of Thixokon.* Clinical reports by Kaufman and Russell[8, 9] and by Denman[10] indicate that this medium fulfills a definite need in urethrography. Ian M. Thompson[11] and James F. Glenn,[12] in papers published in October 1958, also report excellent results with this new medium in extended series of cases. In a formulation of this type it is desirable to have a thickening agent that is completely metabolized or eliminated from the system should the material inadvertently enter the blood stream. In Thixokon this problem is met uniquely

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* Mallinckrodt Chemical Works.

TABLE 3

THICKENED SOLUTIONS OF WATER-SOLUBLE (UROGRAPHIC) MEDIA AND THE TECHNIQUES FOR WHICH THEY ARE APPROVED

Trade name*	Composition	Recommended applications
Salpix (Ortho)	53% w/v Aqueous solution of sodium 3-acetamido-2,4,6-triiodobenzoate plus polyvinylpyrrolidone	Hysterosalpingography
Thixokon (Mallinckrodt)	50% Aqueous solution of sodium 3-acetamido-2,4,6-triiodobenzoate plus amioca starch	Urethrography and cystography
Skiodan Acacia Solution (Winthrop)	40% Skiodan with 20% w/v acacia	Uterosalpingography
Medopaque-H (Bell-Craig)	Aqueous solution of sodium *o*-iodohippurate 35%, sodium iodide 10% plus polyethylene glycols	Hysterosalpingography, cholangiography, sinuses, fistulas, and empyema cavities

* Name in parentheses is that of manufacturer. Addresses of those not given in footnotes to the text are as follows: Ortho Pharmaceutical Corporation, Raritan, N. J., and Bell-Craig Inc., New York, N. Y.

by the use of amioca starch, which is converted to glucose by the enzymes of the body fluids.

One is impressed by the number of nonurographic uses to which the water-soluble media have been put. Henry P. Pendergrass[13] and his associates recently stated that in the Department of Radiology of the Hospital of the University of Pennsylvania, Philadelphia, Pa., about 18 per cent of their supply of urographic contrast material is employed for other special purposes. This may not hold true for all institutions, of course. In TABLE 4 I have indicated the approved techniques for which the urographic materials in one or another of their multifarious forms are now employed; I have included uses of the thickened solutions. The first section of TABLE 4 lists the urographic procedures that depend upon the excretion function of the kidneys. The techniques that involve direct placement of the media are listed in the second section; in the third group are the various vasographic procedures. Our list would be much longer, of course, if we were to include the numerous experimental applications. The situation is reminiscent of an earlier period of radiography when the iodinated oils were the only liquid media and were used, at least experimentally, in so many parts of the body, only to be displaced later by more suitable agents. We may expect that in time new contrast media will be developed that are more specifically designed to meet the requirements of some of the techniques listed in TABLE 4.

Vasography

When a natural collecting or concentrating mechanism is lacking, and direct instillation of a contrast medium is impossible, the vasographic technique may sometimes be used. The accepted procedures listed in TABLE 4 comprise many variations developed and extended by many ingenious radiologists. The

TABLE 4

TECHNIQUES FOR WHICH ONE OR MORE OF THE WATER-SOLUBLE (UROGRAPHIC) CONTRAST AGENTS ARE RECOMMENDED

- Techniques depending upon the excretion function of the kidneys:
    - Intravenous urography
    - Subcutaneous urography
    - Intramuscular urography
- Techniques involving direct placement of contrast agent:
    - Retrograde pyelography
    - Cystography
    - Urethrography
    - Intraductal cholangiography
    - Visualization of sinuses
    - Hysterosalpingography
    - Visualization of fistulas
- Vasographic techniques:
    - Angiocardiography
    - Translumbar arteriography
    - Nephrography
    - Cerebral angiography
    - Arteriography (peripheral)
    - Venography
- Other applications:
    - Gastrointestinal roentgenography

opaque media employed are generally the water-soluble urographic media. It is not my purpose to review this extensive field, but merely to emphasize its importance and to suggest that advances and expansions in the use of contrast media in the immediate future are likely to be made through vasography. At present, many of the vasographic techniques are practiced only in the larger institutions or teaching hospitals. As the necessary equipment and trained personnel become widely available, examinations using this technique may become more common.

Wanted: New Contrast Media

The X-ray examination of many regions of the human body is unsatisfactory or impossible with existing media or techniques. In the intravenous procedures thus far mentioned, natural physiological processes of excretion or concentration are operative in only two cases: urography and cholecystography (and the related intravenous cholangiography). Another collecting mechanism is the phagocytic action of certain cells of the liver and spleen in removing colloidal or particulate matter from the blood. The use of colliodal thorium dioxide (Thorotrast*) in hepatolienography is based on this principle. Other suspensions and colloids have been tried in the United States and in Europe but, at present, only Thorotrast is employed for this technique; it is also used for lymphangiography, cerebral angiography, and several other vasographic techniques. Its intravascular use is restricted by its slight radioactivity and by the fact that it is not absorbed from its sites of accumulation in the liver and spleen. After some time it may produce fibrosis. The manufacturer cautions that Thorotrast be used only where life expectancy is considered to be relatively short and where other agents are unsatisfactory.

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* Product of Testagar & Co., Inc.

For reasons stated above many attempts have been made to find a substitute for Thorotrast. Excellent reviews and accounts of original work can be found in the paper by Thomas *et al.*,[14] which appeared in 1951, and in the more recent one by Berger[15] in 1956. H. W. Fischer[16] reported in 1957 on the use of colloidal stannic oxide in opacifying the liver and spleen in animals. Several investigations have been reported on the use of emulsions of ethyl di- and triiodostearate and emulsions of other iodinated oils.[14, 15] The rather severe side reactions were attributed partly to variability and instability of the emulsions and to the fact that metabolism liberates objectionably large amounts of iodide within the body. Recently F. S. Hom *et al.*[17] at Temple University in Philadelphia, Pa., described the preparation of very stable emulsions of Ethiodol.* Pharmacological and clinical studies have not been published.

The Swedish radiologists Olsson and Ekman[18] administered brominated fatty esters to cats and, after several hours, noted satisfactory opacification of the liver. These investigations and those previously cited suggest that ultimately we shall have suitable media for diagnostic examination of both the liver and spleen.

The fact that certain organs or tissues selectively adsorb or collect detectable amounts of specific substances such as dyes has frequently raised false hopes of obtaining a diagnostically valuable radiopaque medium by introducing iodine into the specific compound adsorbed. However, the quantity of dye adsorbed is usually so small that it could not cast a shadow even it if were 100 per cent iodine. Furthermore, the introduction of iodine into the compound frequently so alters its properties that it is no longer specifically adsorbed by the tissue or organ.

An entirely new type of medium is envisioned by Charles T. Dotter[19] of the University of Oregon Medical School, Portland, Ore. In cardiovascular studies in animals, Dotter uses an opaque medium in the form of discrete particles. During roentgenography, these particles produce an effect like "snowflakes in a headlight beam." X-ray exposures of accurately timed duration and sequence are made. Dotter points out that by this means it should be possible to observe blood turbulence within the heart and blood vessels and to measure blood flow and cardiac output. By counting the particles it should be possible to determine the relative flow of blood into the various branches of the pulmonary artery. Although prodigious technical problems remain to be solved, Dotter hopes that this technique will soon be applied to man.

Unfavorable Sequelae

The question may be asked: Have today's water-soluble contrast media attained the ultimate in safety? Probably not, but further progress may be difficult. The acute toxicity (LD_{50}) of some of these media as measured in animals is more than 10 gm./kg. of body weight, comparable in magnitude to that of glucose used for intravenous feeding. At these high dosage levels, such factors as concentration and rate of injection are important and make exact determinations or comparisons difficult. If a pharmacologist wished to be facetious, he might conceivably retard the rate of injection sufficiently to equal the rate of excretion and thus permit continuous injection. The test animal would then be "on stream," as the engineers say, and the pharmacologist could report an infinite LD_{50}.

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* Product of E. Fougera & Co., Inc.

Of serious concern are the occasional severe reactions encountered after intravenous injection of X-ray contrast media. Accurate and comprehensive data are difficult to obtain because of the understandable reluctance of physicians and manufacturers to discuss their experiences in this connection. The latest reports were published in *Radiology* in July 1958.[13, 20-23] One should refer to these papers for the most recent information on the occurrence of unfavorable reactions and their treatment. It is encouraging to note from the tabulations for the period 1953 to 1957 that fatal reactions have not increased out of proportion to the increased number of radiographic examinations performed.

S. William Simon and his associates[24] and Sanger and Ehrlich[25] reported that simultaneous injection of an antihistamine diminished the reactions to contrast agents. On the other hand, Finby *et al.*[21] stated recently that, in their hands, antihistamines (orally or intravenously administered) have not been successful in preventing major reactions and that the addition of any intravenous agent, especially when mixed with the contrast medium, adds still another source of reaction. The many investigations published during the last ten years leave undecided the question as to whether premedication with antihistamines significantly diminishes the side reactions from urographic agents.

For several years a group at Duke University School of Medicine, Durham, N. C., has studied the effect of contrast media upon nerve tissue, an important consideration in such techniques as aortography and cerebral angiography. In a continuation of their study, two papers appeared in 1958 that may point the way toward counteracting such action on the nerves. Kenan *et al.*[26] found that glucose and procaine exhibited a remarkable protective effect against injury to the spinal cords of dogs. In another paper, Huger *et al.*,[27] also reported that, in their work with dogs, intraaortic injection of procaine prevented significant injury.

The few investigations I have cited illustrate the serious study being devoted to the problem of side reactions. Progress that we may note here and there, although it may not be substantiated completely by later workers, will lead inevitably to fresh theoretical approaches. We may hope for eventual reductions in the number and seriousness of reactions.

Other Opaque Elements

Are we limited to iodine and the few other elements of which our present radiopaque media are composed? The physicists tell us that increased absorptivity to X rays is obtained with elements of higher atomic number. The elements oxygen, nitrogen (air), and a few other gases are used in radiography because of their nonabsorption of X rays. Within the limits of wave length usable in radiography, bromine (atomic number 35) is less opaque than iodine (atomic number 53). Yet calcium, with the low atomic number of 20, causes bones to cast a shadow. I should not care to predict a lower limit of atomic number for usefully opaque elements. With elements at the upper end of the atomic scale above bismuth (atomic number 83) we encounter undesirable radioactivity. The majority of metallic elements in their ionic forms are relatively toxic; we speak of "heavy metal poisoning." To be useful, elements presumably must be insoluble (for example, barium sulfate) or be an innocuous colloid or chelate. Other contributions to this monograph present information on advances along these lines. Iodine still remains the most versatile element for incorporation into opaque media. Its ability to enter into organic combinations makes possible the synthesis of a great variety of iodine-containing compounds that can be modified in innumerable ways while retaining the radiopacity of the iodine.

Our list of contrast media comprises twenty radiopaque chemical substances offered in more than sixty forms or formulations. We have noted recent additions to each of the major groups: G.I. media, oils and suspensions, cholecystographic agents, and the water-soluble urographic materials. Adequate transport or collecting mechanisms are operative in G.I. roentgenography, cholecystography, urography and, less satisfactorily, in hepatolienography. Other techniques are dependent upon direct placement of the medium or upon the vasographic approach. There are many opportunities for new media, not only for the techniques that are approved and widely used, but also for new radiographic procedures now in the experimental phase.

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CHEMICAL ASPECTS OF RADIOPAQUE AGENTS

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In considering the design of any radiopaque compound, the chemist must keep in mind the fact that the architect's dictum that "form follows function" applies equally well to him. The form that the drug will eventually take will be shaped by the following major criteria:

(1) The compound must be opaque to X rays. Only the heavier elements absorb sufficiently in the diagnostically useful region of the X-ray spectrum. Iodine has become the element of choice because it has adequate absorption characteristics at voltages normally used and can be incorporated readily into a wide variety of organic molecules.

(2) The drug must concentrate in the organ to be visualized. This is most easily accomplished by direct instillation, but for a large proportion of radiological work indirect instillation is required.

(3) The drug must be nontoxic. Ideally, signs of frank toxicity and pharmacodynamic effects should be absent.

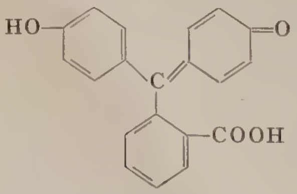
It is convenient to classify radiopaques according to their physical properties and routes of administration.

Directly instilled radiopaques may be subdivided into (1) water-soluble compounds, including those used in operative cholangiography, myelography, and bronchography; and (2) the widely used water-insoluble compounds including barium sulfate and the iodized oils.

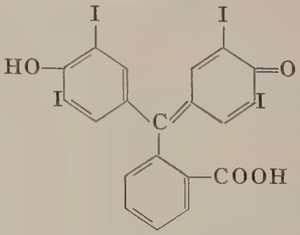
Indirectly instilled compounds may also be subdivided into water-soluble and water-insoluble compounds, the former broad class including (1) substances used in such techniques as urography, angiography, cerebral angiography; the latter (2) including cholecystographic agents as the most important members of the group.

In general it may be said that it is relatively easy for the chemist to prepare directly instilled compounds that fulfill the first two general criteria. It is the toxicity and other special requirements that present the challenges to the investigator.

The indirectly instilled compounds have occupied the attention of a number of workers in recent years. Significant advances have emerged as a result of this effort. This article will deal solely with the cholecystographic agents, since the other classes are reviewed elsewhere in this monograph.

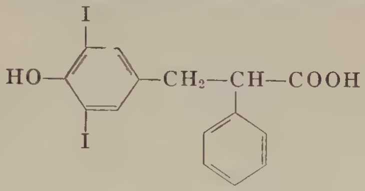


Phenolphthalein



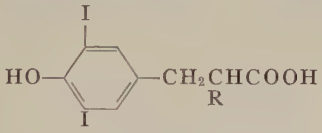
Tetraiodophenolphthalein
(Iodophthalein)

About 1925 Graham and Cole[1] capitalized on their prior observation that phenolphthalein is concentrated in the bile by preparing and studying the corresponding tetraiodo derivative, thereby supplying radiologists with the first clinically useful cholecystographic agent. Despite its very obvious shortcomings this remained the drug of choice in the United States until about 1943, when another agent, Priodax,* was introduced.[2] This development represented a major advance from the chemical point of view, since the molecule contained only 2 instead of 4 atoms of iodine but furnished superior cholecystograms.



Iodoalphionic acid (Priodax)

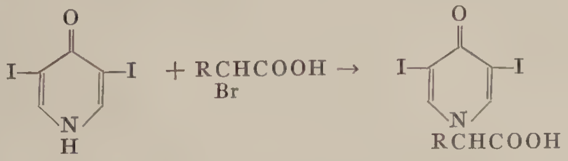
In 1946 Epstein *et al.*[3] made the first attempt to correlate structure with cholecystographic activity in a series of diiodohydroxyphenylalkanoic acids, as shown in the general structure of formula I. It can be seen that when $R = C_6H_5$, the compound is iodoalphionic acid. These authors observed that in



(I)

dogs the lower members of the series ($R = CH_3$ or C_2H_5) were not concentrated in the gall bladder, but appeared in the urinary bladder instead. Alkyl groups of moderate size ($R = C_4H_9$) directed the drug to the gall bladder, while higher members were not absorbed from the intestinal tract. The investigators felt also that the hydroxyl group assisted in some way in promoting concentration of the drug in the bile.

It seemed to us that in an analysis of the structure-activity relation two questions required consideration. First, what were the structural features necessary to promote intestinal absorption of an orally administered drug and, second, what were the requirements for good concentration in the gall bladder? To show that these were indeed separate questions, we studied the higher homologues of another compound, Diodrast,† having the general structure of formula II.[4] The compounds were prepared according to the equation:



(Diodrast)

(II)

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* Product of Schering Corporation, Bloomfield, N. J.

† Product of Winthrop Laboratories, New York, N. Y.

All members of the group were first administered orally to cats and none appeared to be absorbed from the intestine. Fortunately, most of the series were sufficiently nontoxic to be administered intravenously. When this was done it was found that the lower members were excreted in the urine and the higher members appeared in the bile. The transition point was reached when the alkyl group was propyl (II, $R = CH_3CH_2CH_2$). It was possible to visualize both the gall and urinary bladders with this compound.

We then turned our attention to oral cholecystography. A method for quantitatively comparing potential contrast media was developed by Hoppe,[5] who used the cat as the experimental animal. A standard series of films using graded doses of iodoalphionic acid was first obtained. These were rated as absent, poor, fair, good, and excellent. Numerical values were assigned to each grade to facilitate the comparisons, and ratings were then made as per-

TABLE 1

BILIARY CONCENTRATION IN CATS OF AMINODIIODOPHENYLALKANOIC ACIDS

Compound	Iodoalphionic acid
	(percentages)
Iodoalphionic Acid	100
III, R =	
CH_2CH_3	90
$CH_2CH_2CH_3$	90
$CH_2CH_2CH_2CH_3$	108
$CH_2CH_2CH_2CH_2CH_3$	30

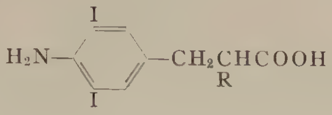
TABLE 2

CHOLECYSTOGRAPHIC ACTIVITY OF AMINODIIODOPHENYL CARBAMIDO AND SULFONAMIDO ALKANOIC ACIDS

Compound	Iodoalphionic acid
	(percentages)
III, R =	
CH_3	25
$CH_2CH_2CH_3$	25
$CH_2CH_2CH_2CH_3$	75
$CH_2CH_2CH_2CH_2CH_3$	120
$CH_2CH_2CH(CH_3)_2$	103
C_6H_5	0
C_6H_{11}	20
$C_6H_5CH_2$	62
IV, R =	
CH_2CH_3	87
$CH(CH_3)_2$	108
$CH_2CH_2CH_2CH_3$	110
$CH_2CH(CH_3)_2$	96
$CH_2CH_2CH_2CH_2CH_3$	72
C_6H_5	48
$C_6H_5CH_2$	102
C_5H_9 (cyclopentyl)	120

centages of the standard—iodoalphionic acid. In preliminary examination a dose of 100 mg./kg. was used.

We studied a group of compounds analogous to those of Epstein *et al.*[3] except that the hydroxyl group was replaced by an amino function, giving the general formula III.[6]

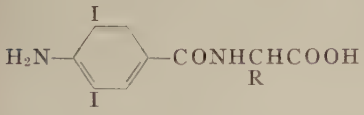


(III)

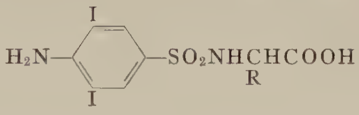
The results are summarized in TABLE 1.

It was concluded that, contrary to earlier opinion, the hydroxyl group was not necessary for good visualization, and that the sole function of this group was a chemical one: namely, to facilitate introduction of the iodine atoms into the aromatic ring. The earlier observation that activity reached a maximum when the alkanoic portion of the molecule was of moderate size was confirmed.

We were interested in assessing the importance of the methylene group in formula III that joined the aromatic moiety to the alkanoic acid. For this purpose we examined 2 series of compounds represented by formulas IV and V:



(IV)



(V)

in which the methylene of III was replaced by a carbamido and sulfonamido group, respectively (TABLE 2).

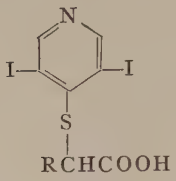
In general, the results were similar to those found in the other series. Again a maximum was reached with a moderately large alkanoic acid residue. The sulfonamido series was inherently more active than the carbamido group.

In the next study, not only was a new bridging group introduced, but the aromatic ring was heterocyclic and devoid of either an amino or hydroxyl group. A small series represented by formula VI was prepared and examined with the results shown in TABLE 3.

TABLE 3

CHOLECYSTOGRAPHIC ACTIVITY OF A SERIES OF 2-(3,5-DIIODO-4-PYRIDYLMERCAPTO)-ALKANOIC ACIDS

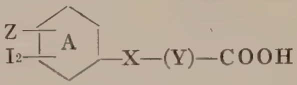
Compound	Iodoalphionic acid
	(percentages)
VI, *R* =	
$CH_2CH_2CH_3$	112
$CH_2CH_2CH_2CH_3$	120
$CH_2CH_2CH(CH_3)_2$	90



(VI)

Thus it was shown that not even the benzene ring was necessary for good activity.

Most of the diiodinated compounds reported may be formulated as members of a broad class formulated as in formula VII:



(VII)

where Z represents H, NH_2, or OH; X is CH_2, S, CONH, SO_2NH, or CH=CH; Y represents the lipophilic group; and A represents the aromatic ring.

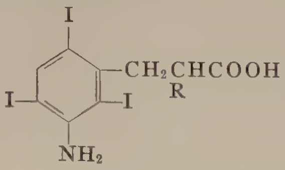
The nature of Z has little effect on cholecystographic action. Its prime purpose is to allow easy introduction of the iodine atoms. If this can be done in other ways, so that Z represents H, activity still persists. Our pyridylmercaptoalkanoic acid series illustrates this point and further shows that the benzenoid ring per se is dispensable. The aromatic ring functions as a carrier for relatively metabolically stable iodine atoms.

On the other hand, it was repeatedly demonstrated that the lipophilic group Y is of extreme importance. It is the variation in this portion of the molecule that exerts the most profound effect on the activity of the contrast medium. When Y is too large, as in the case of Epstein's[3] higher members, poor visualization results. When this group is too small, the drug is either not absorbed from the intestinal tract or is excreted through the kidneys. Variation of the bridging group exerts minor rather than major effects on biliary concentration.

As a result of this analysis it was concluded that the essential features of a good gall bladder contrast agent are (1) a high iodine content to visualize the gall bladder, (2) a lipophilic group of moderate size to distribute the drug properly, and (3) achievement of a proper balance between the lipo- and hydrophilic portions of the compound to ensure gastrointestinal absorption.

We felt that all the appropriate variations in the organic parts of the molecule had been made to effect maximum visualization and that it would be fruitless to continue exploration in the diiodo series. Our best compound was only about 20 per cent more effective than iodoalphionic acid. Our hope of increasing effectiveness seemed to lie in the direction of adding more visualizing power to the molecule by increasing the iodine content. Thus, if the features that made a diiodinated substance an effective agent were approximately the same for triiodinated compounds, then the higher halogen content of the latter should raise the ceiling of maximum effectiveness.

A group of compounds of the general structure of formula VIII was prepared and tested for cholecystographic action, as shown in TABLE 4.[5-7]



(VIII)

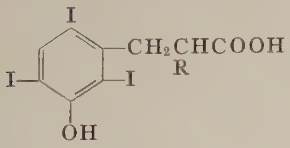
Although maximum activity was reached somewhat sooner than in the corresponding diiodo series, the best far exceeded anything we had seen previously. The most active member (VIII, *R* = C_2H_5) is Telepaque,* whose clinical effectiveness is well established.

This development opened a new era in the field of cholecystography; in recent years other triiodinated compounds (formulas IX to XII) have been introduced clinically. All of these, including Telepaque, can be encompassed within our generalized formula VII, except that now three rather than two iodine atoms are present.

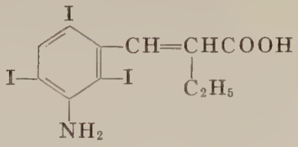
TABLE 4

CHOLECYSTOGRAPHIC ACTIVITY OF THE AMINOTRIIODOPHENYLALKANOIC ACIDS

Compound	Iodoalphionic acid
	(percentages)
VIII, *R* =	
H	56
CH_3	120
CH_2CH_3	144
$CH_2CH_2CH_3$	116
$CH_2CH_2CH_2CH_3$	16



(IX)



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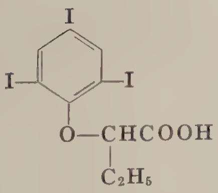

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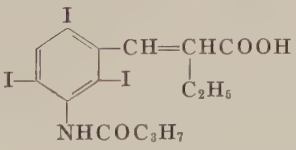

(XII)

It is a curious coincidence that a parallel development was going on in the realm of the water-soluble radiopaques. Hypaque† and Urokon‡ were replacing the diiodinated urographic agents just as Telepaque was replacing iodoalphionic acid in cholecystography; we are now in the era of the triiodinated contrast agents.

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* Product of Winthrop Laboratories, New York, N. Y.
† Product of Winthrop Laboratories, New York, N. Y.
‡ Product of Mallinckrodt Chemical Works, St. Louis, Mo.

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SOME PHARMACOLOGICAL ASPECTS OF RADIOPAQUE COMPOUNDS

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Of the various substances used as radiopaque media, the water-soluble, iodinated, organic class of compounds is of greatest interest from a pharmacological point of view. Not only are these compounds administered intravenously or even intra-arterially; they are given in the form of strongly hypertonic solutions by rapid injection to patients who usually are not in the best state of health. The magnitude of the clinical requirements for this type of compound is illustrated by the fact that 50 cc. of a 50 to 90 per cent solution may be injected in 2 sec. or less. These requirements are in striking contrast to classic pharmacological practice in the administration of drugs. In spite of these unusual requirements, the practical clinical use of this group of compounds is associated with surprisingly few serious reactions.

The essential properties of a useful radiopaque medium include high radiopacity, low systemic and local tissue toxicity, pharmacodynamic silence, selective localization, and prompt and complete elimination. Of these, low toxicity at both the systemic and local tissue levels is the most important and also the most difficult to achieve. It is the purpose of the present communication to examine in some detail the systemic and local tissue toxicity of four of the commonly used in water-soluble compounds (FIGURE 1).

The two compounds shown at the top of FIGURE 1—iodopyracet (Diodrast*) and sodium iodomethamate (Neo-Iopax†)—originated in Germany nearly thirty years ago and still are widely used throughout the world. They resulted from the observation that the iodopyridines used in the treatment of gall bladder infections might also provide a means of outlining the organ in X-ray examinations. Although the gall bladder was not clearly outlined, the definition of the urinary-tract shadows was sufficiently encouraging to stimulate Binz and Rath to find a better tolerated and more soluble iodinated compound. This led to the synthesis of sodium 5-iodo-2-pyridone-N-acetate (Uroselectan‡) and the description of its use for excretion urography by Swick and von Lichtenberg in 1929.[1, 2] Two years later, von Lichtenberg[3] described the urographic properties of iodopyracet (as the sodium salt) and sodium iodomethamate. No serious challenge to the superiority of these 2 compounds appeared until nearly 20 years later, when Wallingford[4, 5] described sodium acetrizoate (Urokon§) which represented a distinct improvement in radiopacity with but little improvement in toxicity. A highly significant improvement in both systemic and local tissue toxicity was achieved in 1954 when diatrizoate sodium was described in this country by Larsen *et al.*[6, 7] and, independently in Germany, by Langecker *et al.*[8]

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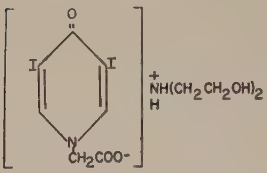
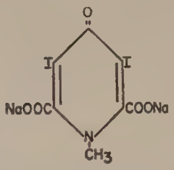
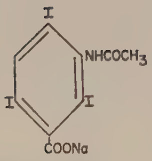
* Product of Winthrop Laboratories, New York, N. Y.
† Product of Schering Corporation, Bloomfield, N. J.
‡ Product of Schering A. G., Berlin, Germany.
§ Product of Mallinckrodt Chemical Works, St. Louis, Mo.



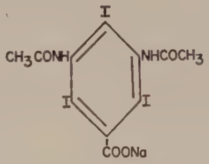
IODOPYRACET
(DIODRAST)
M.W. 510
%I 49.8



SODIUM IODOMETHAMATE
(NEO-IOPAX)
M.W. 493
%I 51.5



SODIUM ACETRIZOATE
(UROKON)
M.W. 578.9
%I 65.8



DIATRIZOATE SODIUM
(HYPAQUE)
M.W. 636
%I 59.87

FIGURE 1. The chemical structure, molecular weight, and percentage of iodine of four of the commonly used water-soluble iodinated, organic radiopaque compounds. Proprietary names are shown in parentheses.

One of the most fascinating suggestions for the synthesis of a urographic contrast medium was made by Swick[9] in 1933 when he proposed the use of the detoxication product of sodium benzoate, hippuric acid, as the carrier for iodine in the synthesis of an effective, nontoxic compound for the X-ray visualization of the urinary tract. Because of systemic side effects, this compound, iodohippurate sodium (Hippuran*) never achieved the extensive clinical use attained by iodopyracet and sodium iodomethamate. Recent studies carried out in our laboratories[10] and summarized in FIGURE 2 seem to offer an explanation for the failure of this compound to live up to the initial expectations. The acute intravenous LD_{50} values, expressed in millimoles per kilogram ± 1 standard error, were determined using 10 mice at 3 or more logarithmically spaced dose levels. It is seen that conjugation of sodium benzoate with glycine reduced the toxicity of sodium benzoate from 10 to 22.6 mmole/kg. The addition of iodine, however, resulted in an increase in toxicity to that of sodium benzoate. Although the addition of the 3-acetamido group was associated with a highly significant reduction in toxicity, the reduction was not as great as that observed with glycine conjugation. The addition of the 3,5-diacetamido groups was associated with a reduction in the toxicity of sodium benzoate similar to that observed with conjugation with glycine. Of particular interest was the observation that the 3 iodines could be added to both the sodium 3-acetamido and the 3,5-diacetamido benzoates with no change in toxicity in terms of millimoles per kilogram. Diatrizoate sodium, therefore, appears to fulfill the requirements of Swick's hypothesis.

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* Product of Mallinckrodt Chemical Works.

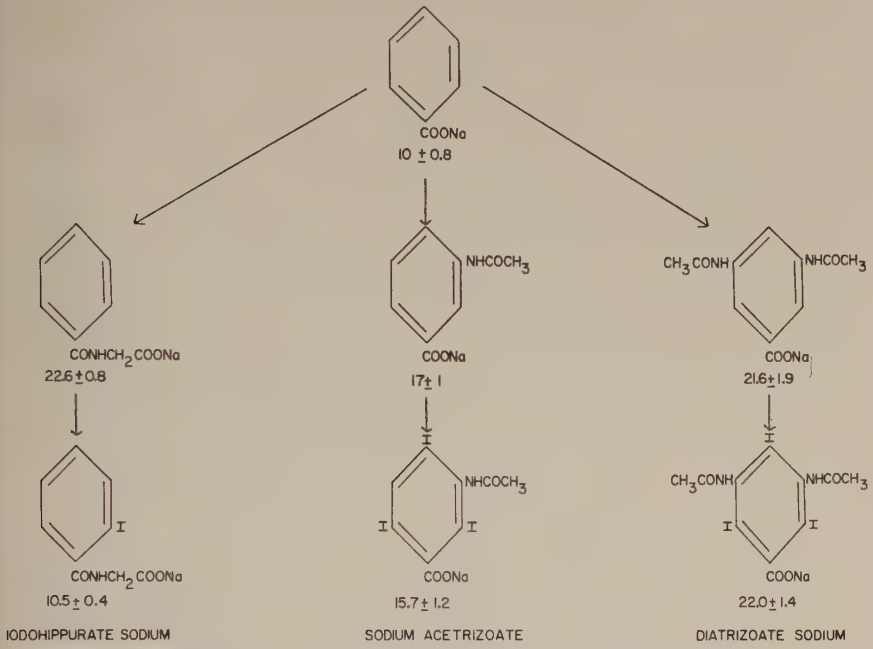

FIGURE 2. The derivation of effective and less toxic radiopaque compounds from detoxication derivatives of sodium benzoate in the mouse. Figures are in millimoles per kilogram.

EXPERIMENTAL

Systemic Toxicity

One of the basic steps in the analysis of the pharmacological properties of a chemical substance is the characterization of the dose-mortality curve in the experimental animal. The nature of this curve is as fundamental an identifying biological property of a chemical substance as is the boiling point or melting point in the characterization of its chemical properties. Shown in FIGURE 3 are the dose-mortality curves for sodium iodomethamate, iodopyracet, sodium acetrizoate, and diatrizoate sodium, obtained following intravenous injection in the mouse. Commercially available solutions—35 per cent iodopyracet and 50 per cent solutions of the other 3 compounds—were injected intravenously at a rate of 1 cc./min., using groups of 10 adult, male, albino mice weighing 20 ± 2 gm. Injections were given at 3 logarithmically spaced dose intervals, indicated by the points on the curves in FIGURE 3. The LD_{50} ± its standard error was calculated for each compound by the log-probit method of Miller and Tainter[11] and is shown in FIGURE 3. In the mouse, the toxicity (from most to least toxic) was found to be as follows: sodium iodomethamate, 4600 ± 470 mg./kg.; iodopyracet, 6300 ± 220 mg./kg.; sodium acetrizoate, 7700 ± 540 mg./kg.; and diatrizoate sodium, 14,000 ± 800 mg./kg. The acute intravenous toxicity of these compounds has also been determined in the rat, rabbit, cat, and dog.[10, 12] The LD_{50} values for iodopyracet were found to vary

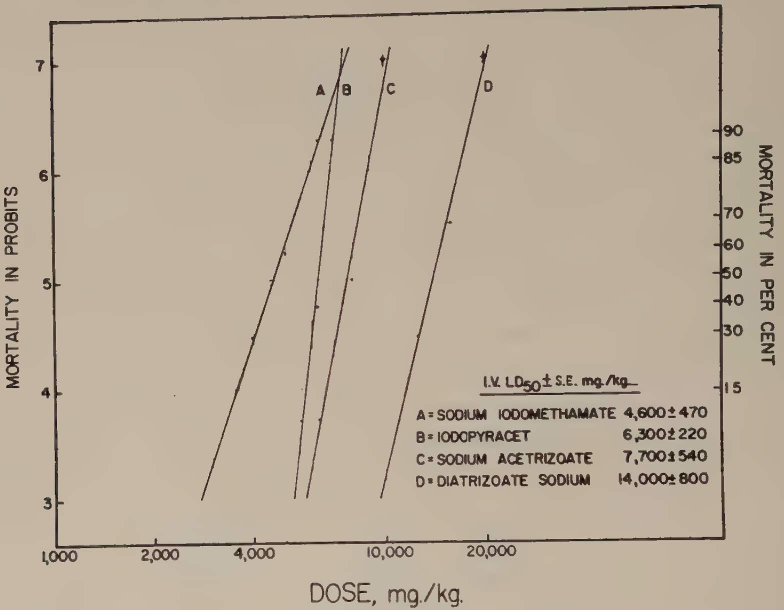

FIGURE 3. Acute intravenous dose-mortality curves in the mouse.

from 2800 to 6400 mg./kg.; for sodium iodomethamate, from 4500 to 7200 mg./kg.; for sodium acetrizoate, from 5200 to 9100 mg./kg.; and for diatrizoate sodium, from 11,300 to 14,000 mg./kg. The smallest species variation was observed with diatrizoate sodium and sodium iodomethamate.

As illustrated by the dose-mortality curves in the mouse, the relationship between dose and mortality for each of these compounds is sharp and clearly defined. No symptoms of systemic intoxication were observed until the dose-mortality range was entered. When this was done, the mortality rate rose very steeply as the dose was increased within narrow limits. The steepness of the dose-mortality curves and, in particular, their location in the several thousand milligram per kilogram dose range make it possible to use these compounds in such large dosages with relative freedom from serious toxic effects.

The symptoms observed at death in the experimental animal can be divided into two major categories: convulsions and capillary breakdown in the lungs.

Convulsions. As the lethal dose range is approached, the animal appears to become apprehensive. Vomiting (except in the rodents), urination, and defecation invariably occur. Generalized muscular twitching followed by muscular incoordination and clonic convulsions appear. The convulsions are severe and may last from 2 to 10 min. to as long as 3 to 6 hours. As the dose is increased, convulsions may appear during or immediately after completion of the injection; these terminate in a series of clonic-tonic convulsions and death, following respiratory arrest 3 to 15 min. after injection. The majority of deaths occur in the first 3 hours after injection, with a few occurring overnight. For this reason the LD_{50} values are calculated at 24 hours after injection.

Capillary breakdown in the lungs. A froth tinted with fresh blood invariably appears at the external nares during the later stages of convulsions that terminate in death. When the thorax is opened immediately after cessation of respiration, the heart is observed to be dilated and beating feebly. Upon opening the pericardium, the right heart fills with blood to nearly twice normal size, and the left heart is usually empty. The lungs are extensively hemorrhagic in appearance and engorged with blood. There is little resemblance to normal lung tissue; the lobes look very much like the lobes of the liver in color and surface appearance. Venous blood mixed with air oozes rapidly from the freshly cut surface. The bronchi and trachea are usually filled with a bloody froth. Venous blood returning to the heart has been pumped to the lungs but, because of the breakdown in the capillary bed in the lungs, it is unable to return to the left heart. In the experimental animal, death appears to be due to a combination of the convulsions and the massive breakdown of the pulmonary vascular bed, with consequent right heart failure preceded by respiratory arrest.

Local Tissue Toxicity

Marginal ear vein of the rabbit. The local irritant effects of these compounds cannot be measured by conventional methods such as the rabbit eye and intradermal trypan blue tests because of the difficulty in differentiating between actual local tissue toxicity and the effects of hypertonicity.[13] It was found possible to differentiate among clinically useful concentrations of these compounds by employing the marginal ear vein of the rabbit as a test organ.[10] A dose of 1.0 cc. of the commercially available solutions was injected once daily for 10 consecutive days into the marginal ear vein of 2 rabbits; the results are summarized in FIGURE 4. Normal saline was used as a control. Sodium iodomethamate, 75 per cent, caused stasis and occlusion of the marginal ear veins of both rabbits, while the 50 per cent concentration caused some stasis in at least 1 marginal ear vein. Iodopyracet and sodium acetrizoate at 70 per cent concentration produced stasis and partial to complete occlusion in at least 1 ear vein. The effects of iodopyracet, 35 per cent; sodium acetrizoate, 30 per cent; and diatrizoate sodium, 50 per cent on the marginal ear vein of the rabbit were negligible and were indistinguishable from those observed with repeated injections of normal saline.

Blood-brain barrier of the rabbit. The effects of these compounds on the blood-brain barrier of the rabbit were studied by means of a modification[14] of the technique described by Broman and Olsson,[15] with results as summarized in FIGURE 5. For each test solution, twenty-five cc. of undiluted commercial solution was injected at a rate of 1 cc. every 2 sec. into the common carotid of at least 5 and as many as 60 rabbits under pentobarbital. Sodium iodomethamate, 50 per cent, and iodopyracet, 70 per cent, produced extensive extravasation of trypan blue, indicating marked breakdown of the blood-brain barrier. Sodium acetrizoate, 50 per cent, produced complete disruption of the cerebral circulation, leading to stasis and hemorrhage into the subarachnoid space. Sodium acetrizoate, 30 per cent, produced only slightly less serious injury, characterized by extensive extravasation of trypan blue similar to that observed

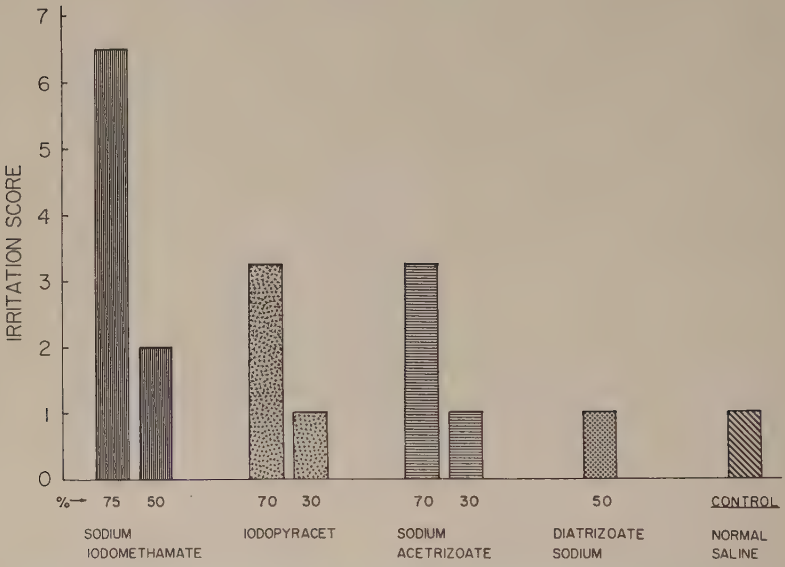

FIGURE 4. Irritancy as measured by means of the marginal ear vein of the rabbit. Scores are maximum average irritation after 10 consecutive daily injections of 1.0 cc. each.

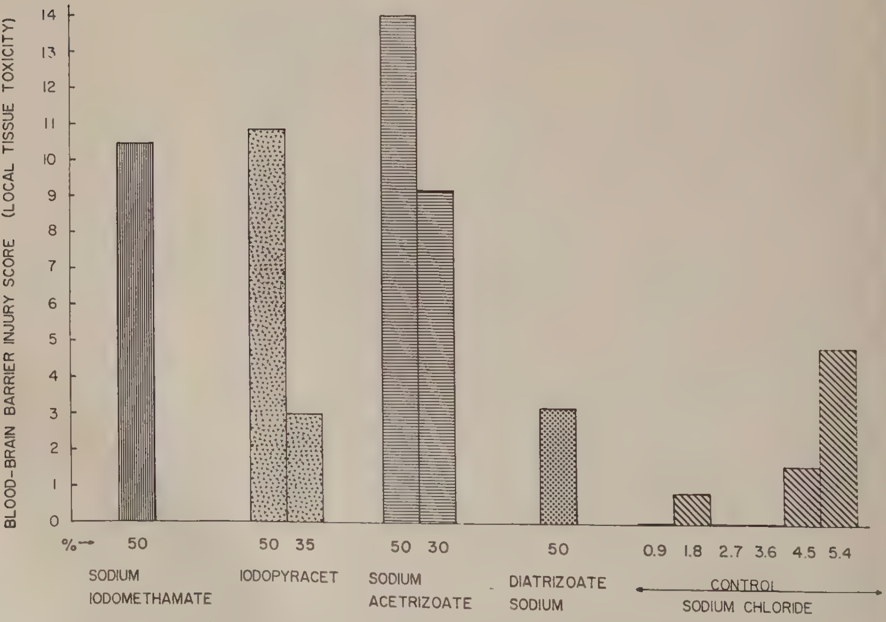

FIGURE 5. The measurement of injury to the blood-brain barrier of the rabbit.

with sodium iodomethamate, 50 per cent. Distinctly less injury to the blood-brain barrier was observed with iodopyracet, 35 per cent, and diatrizoate sodium, 50 per cent, which produced only slight staining of the ipsilateral hemisphere. The degree of injury associated with extravasation of trypan blue does not appear to be due only to hypertonicity, in view of the fact that hypertonic saline at 2, 3, 4, and 5 times the concentration of normal saline injected under the same conditions produced no or only slight staining of the injected side. When the concentration of sodium chloride was increased to 5.4 per cent, or 6 times the concentration of normal saline, the blood-brain injury score began to increase in a manner similar to that observed with the radiopaque compounds. The general resistance of the blood-brain barrier of the rabbit to breakdown with these compounds is illustrated by a comparison of the dosages employed in relation to brain tissue mass. The mean weight of the rabbit brain as estimated from the 280 rabbits used in these experiments was 10 gm. In comparison with the brain of man, taken at 1500 gm., the volume of solution necessary to demonstrate these quantitative differences in local tissue toxicity is estimated to be equivalent to 3750 cc. injected into the common carotid in man at a rate of 1 cc. every 2 sec. These dosages are 250 to 1000 times the volumes customarily employed for cerebral angiography in man.

Beyond the blood-brain barrier. In view of the enormous dosages of these compounds required to demonstrate objective evidence of breakdown of the blood-brain barrier in the rabbit, it became of interest to examine their effects when they were deliberately introduced beyond the blood-brain barrier directly into the cerebrospinal fluid. In striking contrast to the pharmacodynamic silence observed with several thousand milligrams per kilogram when injected intravenously, these compounds produced violent convulsions and death following respiratory arrest when injected into the cerebrospinal fluid at the cisterna magna at doses of 5 to 20 mg./kg. in the rabbit, cat, and dog. In the initial experiments, these compounds were injected at clinical-use concentrations. It was thought that the reactions observed were due to hypertonicity. The solutions were diluted to 10 per cent, which is the approximate isotonic concentration for iodopyracet, sodium acetrizoate, and diatrizoate sodium, as determined by the freezing-point depression method. The isotonic concentration of sodium iodomethamate was found to be approximately 5 per cent.[1] The reactions were equally as prominent at 10 per cent concentration as they were at 35 to 50 per cent concentrations. In fact, hypertonicity per se appeared to be unrelated to the reactions observed intracisternally, since neither convulsions nor death were produced by sodium chloride or sucrose at concentrations up to 6 times the isotonic concentration injected in a volume of 0.5 cc.

Shown in TABLE 1 is a comparison of the approximate LD_{50} estimated following aseptic injection of sterile 10 per cent solutions at the cisterna magna of the rabbit with that estimated following intravenous injection of 35 per cent solution (in the case of iodopyracet) and 50 per cent solutions of each of the other three compounds. In contrast to the 4700 mg./kg. to 12,200 mg./kg. observed after intravenous injection, the LD_{50} values following intracisternal

TABLE 1

A COMPARISON OF THE ACUTE LD_{50} VALUES OBTAINED BY INTRAVENOUS INJECTION AND INJECTION INTO THE CISTERNA MAGNA OF THE RABBIT

Compound*	Intravenous injection $LD_{50} \pm$ S.E.		Intracisternal injection $LD_{50} \pm$ S.E.		
	Number of animals	Mg./kg.	Number of animals	Mg./kg.	Ratio: $\frac{\text{intravenous}}{\text{intracisternal}}$
Iodopyracet (Diodrast)	15	4,700 ± 290	20	13.0 ± 3.7	362
Sodium iodomethamate (Neo-Iopax)	15	5,100 ± 630	20	12.5 ± 2.6	408
Sodium acetrizoate (Urokon)	15	5,200 ± 600	20	7.9 ± 1.4	658
Diatrizoate sodium (Hypaque)	15	12,200 ± 600	20	8.4 ± 2.2	1,452

* Proprietary name is shown in parentheses.

injection ranged from 7.9 mg./kg. to 13.0 mg./kg. The ratio of the LD_{50} value obtained by intravenous injection compared with the value obtained by intracisternal injection was 362 with iodopyracet, 408 with sodium iodomethamate, 658 with sodium acetrizoate, and 1452 with diatrizoate sodium. The relationship between dose and mortality following intracisternal injection was observed to be a function of body weight, and the dose-mortality curves for each compound appeared to be similar to those obtained by intravenous injection in the rabbit. The pattern of the reactions following intracisternal injection also resembled the convulsion phase of the acute toxicity symptoms described under systemic toxicity. Pulmonary circulatory changes were not seen in any of the rabbits. Apprehension, defecation, urination, generalized muscular twitching, and vigorous clonic convulsions were observed within 2 or 3 min. to one-half hour after injection. At the higher dose levels, clonic convulsions progressing into clonic-tonic convulsions terminating in death following respiratory arrest were observed in the majority of the rabbits in 3 min. to 3 hours after injection. An occasional death occurred overnight. The LD_{50} values were also calculated at 24 hours after intracisternal injection.

DISCUSSION

The water-soluble, iodinated, organic class of compounds used as X-ray contrast media possess an unusually low toxicity at both the systemic and local tissue levels in comparison with most pharmacological reagents. The fact remains, however, that reactions ranging from venospasm to convulsions and death do occur. The serious reactions, fortunately, are extremely rare. The July 1958 issue of *Radiology* carried a series of 5 papers devoted to a study of reactions to intravenous iodinated organic compounds.[16-20] Pendergrass *et al.*[16] estimate that the total incidence of reported deaths following urography during the period 1942 to 1956 was 8.6 per million urograms. Statistically, a reaction rate of this low magnitude is extremely difficult to detect in the laboratory. The dose-mortality curves in experimental animals are sharply defined and located in the 3000- to 14,000-mg./kg. dose range in contrast to the usual intravenous urographic dose of approximately 200 mg./kg. in man. In view of the fact that these dose-mortality curves in animals represent only a small segment of the total normal frequency distribution curve for the true LD_{50} value and, further, since the statisticians tell us that the normal frequency distribution curve is an asymptote, it is not unreasonable to expect that an occasional fatality will occur in a subject on the extreme end of the curve. The mortality data in animals indicate that the odds against the occurrence of a fatal reaction at the relatively small dosages used clinically would be several thousand to one. The observed mortality rate of 8.6 deaths per million urograms appears to confirm the conclusions derived from the animal mortality data.

From another viewpoint, the mortality rate in the patient who suffers a fatal reaction is 100 per cent. It becomes of importance, therefore, to discover a means of detecting this rare individual who presumably falls in the extreme lower range of the asymptotic part of the dose-mortality curve. The marked difference in mortality between those rabbits administered the compounds in the vascular side and those receiving them at the cerebrospinal fluid side of the blood-brain barrier suggests the possibility that the blood-brain barrier of this patient may possess an intrinsic susceptibility to breakdown that permits the entry of a fatal amount of these compounds into the cerebrospinal fluid. This hypothesis, of course, is based on the assumption that the behavior of these compounds in the cerebrospinal fluid of man is similar to that observed in the rabbit, cat, and dog. The obvious breakdown of the capillary endothelium in the lungs following intravenous injection of 3000 to 14,000 mg./kg. in the experimental animal makes it difficult to avoid the conclusion that disruption of the capillary endothelium could also occur at lethal intravenous dose levels in the cerebral vasculature of animals. The similarity of the terminal convulsive phenomena following intracisternal injection of 5 to 20 mg./kg. of these compounds compared with those observed following lethal dosages administered intravenously in animals would seem to offer additional evidence in support of this conclusion. It is obvious from the dosages of these compounds employed in man that a blood level is never reached that would resemble even remotely the blood concentration at lethal intravenous dose levels in animals. The convulsive phenomena observed in animals have been described in man; the massive disruption of the pulmonary circulation observed in animals apparently has not been observed in man. The possibility that a relationship may exist between permeability of the blood-brain barrier and the severe reactions observed in man focuses attention on the use of the intravenous test dose as a means of searching for the unusually susceptible patient. As in the problem of dealing with the hazards of exposure to radiation, potentially the most effective protection appears to consist of preventing the event from occurring in the first place.

Reactions that are characteristically allergic in nature, such as urticaria and angioneurotic edema, have been described. In their most recent survey of reactions to the iodinated organic contrast media, Pendergrass *et al.*[16] indicate that the majority of the fatal reactions are anaphylactoid in type. If the word anaphylactoid is used in the strict immunological sense of a specific acquired hypersensitivity, then this conclusion would not appear to fit most of the available evidence. The prophylactic use of the antihistamines has not resulted in any major reduction in severe reactions.[21-23] Sandström concluded from a study involving 1557 cases that the secondary reactions caused by the intravenous injection of contrast media were not of the allergic nature generally assumed in the literature. If the word anaphylactoid is used in its literal sense, meaning simply that the reactions observed bear a symptomatic resemblance to anaphylaxis, then this does appear to agree with the available evidence. The term "intrinsic susceptibility" is a more appropriate one in that it is adequately descriptive and, being free of restrictive connotations, permits a broader approach to the problem of etiology and eventual control of these catastrophic reactions. This, then, opens the door to a consideration of the various biological, physical, and chemical factors that could be involved in the production of these fatal reactions. The first possibility to come to mind is the hypertonicity of the solutions involved. Knowledge of the effects of intravenous injection of hypertonic solutions was available long before these compounds were introduced into clinical medicine. In 1925, Hanzlik *et al.*[24] described in considerable detail the effects of both hypo- and hypertonic solutions on the formed elements and the chemistry of the blood. These investigators observed generalized muscular twitching and tremors in dogs injected intravenously with hypertonic solutions of sodium chloride, dextrose, and sucrose. Convulsions were not observed, although the dosages were not increased to lethal dose levels. The reactions resemble, in part, the systemic toxicity picture observed with the intravenous injection of hypertonic solutions of the iodinated organic radiopaque compounds in the present study. The data from the blood-brain barrier studies in the rabbit did not indicate that hypertonicity per se was the primary factor in eliciting breakdown of the blood-brain barrier as judged from the effects observed with hypertonic solutions of sodium chloride and sucrose. Furthermore, the intravenous injection of 50 per cent solutions of sodium acetrizoate and diatrizoate sodium, which are presumably identical in terms of hypertonicity, produced identical symptoms and tissue changes at death, yet these symptoms were produced with 5200 mg./kg. sodium acetrizoate, whereas with diatrizoate sodium more than twice this amount, 12,200 mg./kg., was required to produce the same symptoms in the rabbit. It is conceivable, however, that hypertonicity may initiate the changes in the permeability of the blood-brain barrier while the specific local tissue toxicity inherent in the chemical structure of the individual compound may complete the breakdown of the blood-brain barrier. This could allow introduction of the compound into the cerebrospinal fluid and cause the central nervous system symptoms observed in the experimental animal at lethal intravenous dose levels. It is, perhaps, unnecessary to point out, in view of the intensity of the reactions observed in the rabbit following intracisternal injection of 5 to 20 mg./kg. of the iodinated organic compounds, that this type of compound should not be used for myelography or encephalography in man.

The wide discrepancy between the intravenous and intracisternal LD_{50}s observed in the rabbit indicate that these compounds do not normally pass through the blood-brain barrier in any significant amount. The fact that they are highly dissociated, water-soluble compounds is contrary to the requirements for the passage of drugs through the barrier. Brodie and Hogben[25] and Kurz and Schanker[26] have observed that the blood-brain barrier is preferentially permeable to the un-ionized, lipid-soluble form of foreign organic electrolytes.

In the course of searching for a water-soluble, iodinated organic compound that would permit a lowering of systemic toxicity and an improvement in local tissue toxicity, more than 100 iodinated organic compounds were studied before diatrizoate sodium was found.[12] As the pharmacological and toxicological data were extended from the mouse to the rat, rabbit, cat, and dog, it became increasingly apparent that the acute intravenous toxicity ceiling had been elevated from approximately 6000 mg./kg. to about 12,000 mg./kg. One of the most important fundamental observations to come from these studies was the fact that diatrizoate sodium demonstrated a uniformly low systemic toxicity among the various animal species tested. Its toxicity at the local tissue level among various species likewise was found to be uniformly low. In view of the apparent relationship between breakdown of the blood-brain barrier and the symptoms produced at death following intravenous injection in the experimental animal, it is of interest to examine the properties of diatrizoate sodium in this respect. The tendency of diatrizoate sodium to elicit breakdown of the blood-brain barrier when administered as a 50 per cent solution in relatively massive volume by rapid intracarotid injection in the rabbit was similar to that observed with iodopyracet, 35 per cent, and markedly less than that observed with sodium iodomethamate, 50 per cent, or sodium acetrizoate, 30 per cent. Further confirmation of the reduced tendency of diatrizoate sodium to elicit breakdown of the blood-brain barrier is derived from a consideration of the magnitude of the differences between the intravenous and the intracisternal LD_{50} values in the rabbit. The LD_{50} ratio (intravenous/intracisternal) for diatrizoate sodium was found to be 2 to 4 times as great as that observed with iodopyracet, sodium iodomethamate, or sodium acetrizoate.

SUMMARY

Of the various properties of a water-soluble, iodinated organic type of radiopaque compound, the most important and also most difficult to attain is that of low systemic and local tissue toxicity.

The acute intravenous toxicity values of 4 examples of this type of compound in the mouse, rat, rabbit, cat, and dog were found to range from 2800 to 6400 mg./kg. with iodopyracet; 4500 to 7200 mg./kg. with sodium iodomethamate; 5200 to 9100 mg./kg. with sodium acetrizoate; and from 11,300 to 14,000 mg./kg. with diatrizoate sodium.

The major symptoms of systemic intoxication at lethal dose levels following intravenous injection in experimental animals were characterized by convulsions, massive breakdown of the pulmonary vascular bed with consequent right heart failure, and death following respiratory arrest.

Extensive breakdown of the blood-brain barrier of the rabbit was observed with sodium iodomethamate, 50 per cent; iodopyracet, 70 per cent; and sodium acetrizoate, 50 and 30 per cent. Minimal extravasation of trypan blue was observed with iodopyracet, 35 per cent, and diatrizoate sodium, 50 per cent. The dosages of all 4 compounds necessary to demonstrate breakdown of the blood-brain barrier of the rabbit were 250 to 1000 times that usually employed for cerebral angiography in man.

The acute LD_{50} values following intracisternal injection in the rabbit were found to be of the order of 7.9 to 13 mg./kg. in contrast to the 4700 to 12,200 mg./kg. observed following intravenous injection. Symptoms following intracisternal injection were characterized by clonic-tonic convulsions and death following respiratory arrest. The pattern of the convulsive phenomena resembled those observed at lethal dosages administered intravenously.

Possible relationships between the mortality data in experimental animals and fatal reactions observed in man were discussed. It was suggested, in view of the striking difference in the toxicity of these compounds depending upon whether they are administered on the vascular or the cerebrospinal fluid sides of the blood-brain barrier, that the rare fatal reaction in man may arise from an intrinsic susceptibility to breakdown of the blood-brain barrier by these compounds.

Acknowledgments

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THE PATHOLOGIST AND TOXICOLOGIST IN THE EVALUATION OF THE SAFETY AND METHODS OF DEVELOPMENT OF RADIODIAGNOSTIC COMPOUNDS

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Introduction

In searching for new X-ray contrast media, the pharmacologist, the chemist, the toxicologist, and the pathologist must work closely together as a research team. The work of the pharmacologist and chemist is fairly well understood; the one screens the chemical compounds made and submitted by the other. The role of the toxicologist and the pathologist in this team is not well understood. Their primary functions are to help in the selection of the best compound and to establish its safety prior to clinical investigation. Their studies usually include toxicity experiments comparing the new X-ray contrast media with each other and with commercially available products. Detailed gross and histological examinations of the tissues of animals often indicate which contrast medium is superior, even though several of them may have been equally good in terms of visualization. In addition, the pathologist can contribute his knowledge of the anatomy and histology of the various species of animals used in this kind of research. The toxicologist can sometimes determine the best chemical compound by carefully distinguishing between pharmacodynamic reactions resulting from injections of large doses of the new contrast media in the same and in different species of animals.

In the following report, experiments will be presented indicative of the part the toxicologist and pathologist play in developing new X-ray contrast media.

Experimental

Bronchographic and Lung Tolerance Studies in Cats

Bronchographic properties of new contrast media can be studied easily in several kinds of animals, including the monkey. However, the cat is usually chosen at this institute because of the relative ease of administration of the contrast media and because of the excellent visualization obtained.

Studies on the bronchographic properties and lung tolerance of 2 compounds,* Dionosil Aqueous (50 per cent) and Dionosil Oily (60 per cent), were done to determine the degree of visualization, the rate of elimination, and the amount of gross pathology. Using these data for a standard, new bronchographic agents can be studied and evaluated.

The bronchographic agent was instilled into the trachea of 4 unanesthetized cats placed prone on the X-ray examining table inclined to an angle of 15° from the horizontal. X rays were taken before instillation, at 1 min. after, and at frequent intervals thereafter to estimate the rate of elimination (FIGURE

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* Produced by Glaxo Laboratories Ltd., London, England.

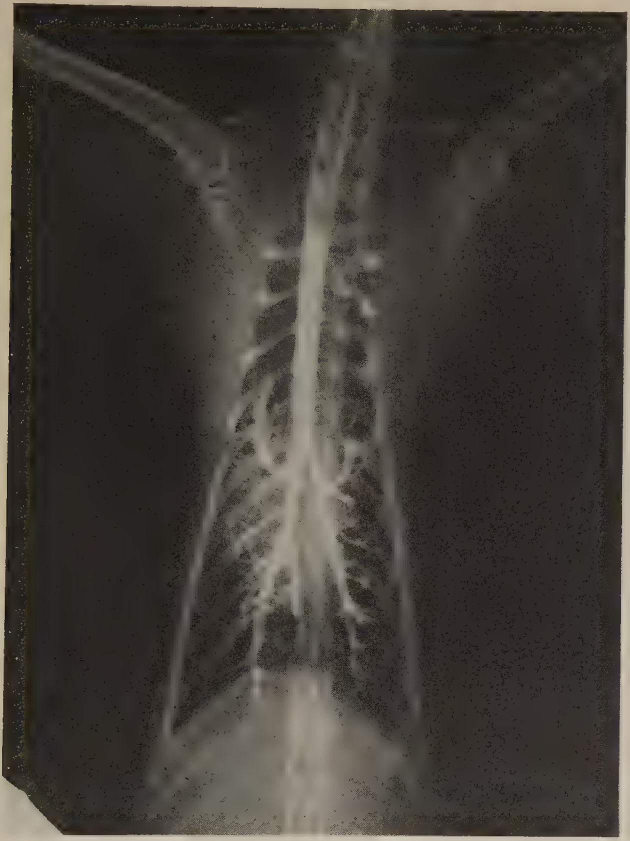

FIGURE 1. Bronchographic visualization at 1 min. after instillation of Dionosil Aqueous in the cat.

1). Two cats from each group were sacrificed at 8 days and the remaining 2 at 28 days for macroscopic and microscopic examination of the lungs, which often were fixed by instilling Zenker formalin directly into the trachea. This technique helped retain the natural structure of the lung without collapse.

Bronchography. Dionosil Aqueous produced fair to excellent visualization with alveolar flooding in 3 of the 4 cats. Elimination of the contrast medium took from 5 to more than 22 days; in other experiments it was often faster. Alveolar flooding usually occurred when Dionosil Aqueous was given to cats; this observation has been confirmed many times (TABLE 1).

Dionosil Oily produced fair to good visualization with no alveolar flooding. Elimination was complete in 2 cats at 24 hours, at 5 days in the third, and after more than 7 days in the fourth cat.

Gross autopsy observations. One of the cats receiving Dionosil Aqueous was observed to have focal bronchopneumonia when examined at autopsy on the eighth day. Chronic inflammation of the lungs at 28 days was found in the

TABLE 1

BRONCHOGRAPHY IN THE CAT WITH DIONOSIL AQUEOUS AND OILY

Preparation	Bronchography						Gross necropsy findings
	No. of days after	Major		Minor		Days for elimination	
		Right	Left	Right	Left		
Dionosil Aqueous	—	0	0	1	1	—	Control plate.
	0	3	2	3	1	5	Fair to good visualization with alveolar flooding in right lobe.
	8	0	0	1	1		Sacrificed at 8 days; lungs normal.
	—	0	0	1	1		Control plate.
	0	3	4	3	1	>7	Good to excellent visualization with alveolar flooding in right side.
	8	0	0	2	1		Slight pneumonia in right middle and upper lobes.
	—	0	0	1	1	—	Control plate.
	0	4	4	1	1	22	Excellent visualization, slow elimination.
	28	0	0	1	1		Sacrificed at 28 days; chronic inflammation with nodule formation left inferior lobe, numerous discrete nodules right inferior lobe.
	—	0	0	0	0	—	Control plate.
	0	2	2	2	2	>22	Fair visualization with alveolar flooding in both sides.
	28	0	0	1	1		Sacrificed at 28 days; small white spot on right upper lobe.
Dionosil Oily	—	0	0	1	0	—	Control plate.
	0	3	3	1	0	>7	Good visualization.
	8	0	0	1	1		Sacrificed at 8 days; slight consolidation in right upper lobe.
	—	0	0	1	1	—	Control plate.
	0	3	3	1	1	5	Good visualization.
	8	0	0	1	1		Sacrificed at 8 days; small 2-mm. spot on right middle lobe.
	—	0	0	1	1	—	Control plate.
	0	2	2	1	1	1	Fair visualization.
	28	0	0	1	1		Lungs normal.
	—	0	0	1	1	—	Control plate.
	0	3	3	1	1	1	Good visualization.
	28	0	0	1	1		Sacrificed at 28 days; lungs normal.

second cat; of the 2 remaining, 1 was normal at 8 days, while the fourth had a small white spot in the right upper lobe. The lungs of the cats receiving Dionosil Oily appeared to be normal at 28 days. At autopsy, 8 days after the instillation, some consolidation in the right upper lobe was observed in 1 cat and a small white spot in the right middle lobe was seen in the second. These white spots were presumed to be the contrast media itself.

Conclusions. Dionosil Oily appeared to be eliminated faster from the lung of cats and caused fewer pathological changes than did Dionosil Aqueous. No alveolar flooding was observed in the cats with Dionosil Oily, whereas it is common with Dionosil Aqueous. Both bronchographic preparations produced good visualization of the lung in cats.

Sciatic Nerve Injection with Tribromoethanol (Avertin) in Cats*

Many attempts have been made to discover effective nerve sclerosing agents. This section deals with an attempt to find not only such an agent, but one that produces also a very dense X-ray shadow. This study illustrates very well the function of the pathologist and toxicologist in helping the pharmacologist to understand more fully what is actually taking place in the animal following medication.

Test solutions. The following solutions were obtained as recent commercial samples or were prepared extemporaneously immediately before injection: (1) tribromoethanol with amylene hydrate; (2) tribromoethanol with amylene hydrate, diluted 1:2 with 95 per cent ethanol; (3) tribromoethanol crystals, dissolved 1 gm./cc. in 95 per cent ethanol; (4) solution 3 diluted 1:2 with 95 per cent ethanol; (5) 95 per cent ethanol; and (6) sterile physiological saline solution.

Procedure. A dose of 0.05 cc. of each solution was injected, under sodium pentobarbital anesthesia, into the sciatic nerve of the left leg in each of 2 cats per sample. The injections were made into the distal third of the nerve under direct observation through surgical exposure of the nerve in the thigh. In each instance the injection was directed peripherally. Immediately after each injection, an X ray was taken for evidence of the extent of injection (FIGURE 2), and again at 6 hours to determine the rate of disappearance of the radiopacity. One cat from each group of 2 was sacrificed after 48 hours for examination of the site of injection and for removal of representative specimens for microscopic tissue examination. The second cat from each group was sacrificed at 7 days after injection, for autopsy and tissue examination of the nerve and surrounding tissues for comparison with the 48-hour observations. The results are summarized in TABLE 2. The tissues were fixed in Zenker formalin, embedded in paraffin, sectioned at 6 μ, and stained by the hematoxylin and eosin method.

Effect on motor function. Complete paralysis of the lower portion of the leg was obtained in every cat injected with each of the solutions except the saline controls.

Radiopacity. Good-to-excellent delineation of the site of injection was obtained with each of the tribromoethanol solutions. The shadows had completely disappeared in the cats injected with the tribromoethanol with amylene hydrate solutions by six hours. After the same period only traces of the radiopaque material were apparent in the cats injected with the tribromoethanol dissolved in alcohol solutions.

Effect on duration of anesthesia. The cats injected with alcohol and saline recovered from the sodium pentobarbital anesthesia overnight and were alert, friendly, and eating on the morning following injection. The cats receiving

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* Marketed by Winthrop Laboratories, New York, N. Y.

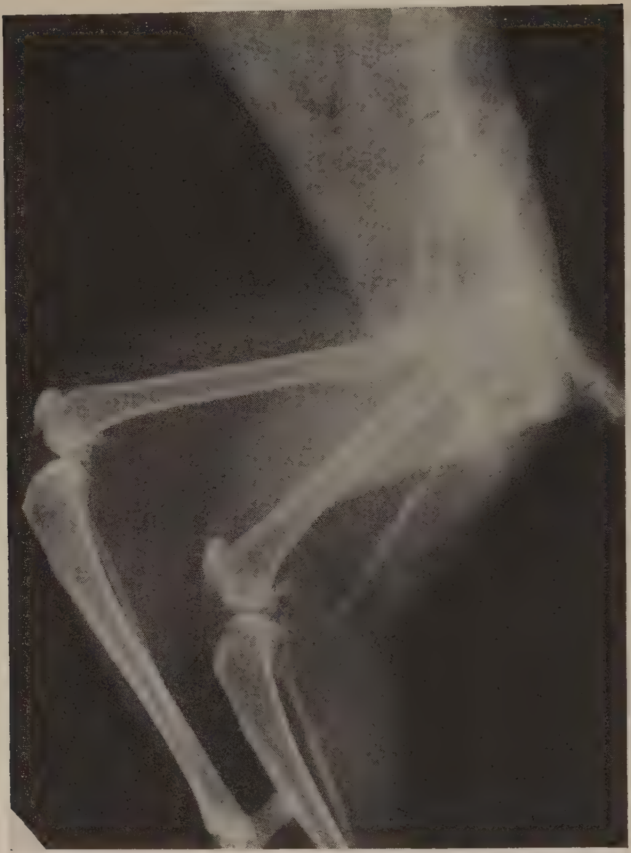

FIGURE 2. Sciatic nerve injection of tribromoethanol in amylene hydrate in the cat.

the tribromoethanol injections, however, were not fully recovered until approximately forty-eight hours after injection.

Intravenous versus intramuscular injection. Since the X ray, in some cases, showed a retrograde flow of the tribromoethanol to within about 2 cm. of the spinal canal, the thought occurred that some of the tribromoethanol had reached the spinal cord and that the prolonged recovery from anesthesia may have been due to an added effect of deep spinal anesthesia caused by the possible presence of tribromoethanol within the spinal canal. To check this point, a dose of 0.05 cc. of tribromoethanol with amylene hydrate was injected intramuscularly into a group of 3 cats and, intravenously, into a second group of 3 cats under sodium pentobarbital anesthesia. Two groups of 2 cats each, for use as controls, were subjected to the sodium pentobarbital anesthesia, but were not given tribromoethanol. The control cats recovered from the barbiturate anesthesia in the usual time, being fully alert and eating on the morning following injection. The tribromoethanol cats, on the other hand, did not fully recover until 46 to 72 hours after injection of the sodium pentobarbital.

TABLE 2

INJECTION OF 0.05 CC. OF AVERTIN SOLUTION INTO THE SCIATIC NERVE OF CATS*

Sample	Radiopacity after injection		Recovery from anesthesia	Autopsy findings†	
	Immediate	6 hr.	hours	Days after injection	Gross observations
Avertin with amylene hydrate, undiluted	4	0	48	2	Minor adhesions, old hemorrhagic spots, edema.
	3	0	48	7	Slight discoloration at site of injection.
Avertin with amylene hydrate, diluted 1:2 with 95% ethanol	3	0	48	2	Very slight hemorrhagic area at site of injection; slight discoloration.
	4	0	48	7	Slight adhesion to muscle, distinct yellowish coloration at site of injection; old blood clot.
Avertin, dissolved 1 gm./cc. in 95% ethanol	4	1	48	2	Large blood clot, edema, yellowish discoloration.
	4	1	48	7	Distinct adhesion to muscle; yellowish discoloration.
Avertin, 1 gm./cc. in 95% ethanol, diluted 1:2 with 95% ethanol	3	1	48	7	Slight but distinct adhesions to muscle; reddish discoloration at site of injection.
	3	1	48	2	Old blood clot, edema, distorted morphology, darkened in color.
95% Ethanol	0	—	<24	7	Adhesion to fat tissue; slight yellowish discoloration at site of injection.
	0	—	<24	2	Hemorrhagic area at site of injection, swelling.
Sterile saline	0	—	<24	2	Normal.
	0	—	<24	7	Normal.

* Two cats in each group.

† Paralysis occurred in injected leg of all medicated cats; no paralysis was observed in saline controls.

Two groups of 3 cats plus 2 controls in each group were injected, without anesthesia, with 0.05 cc. of tribromoethanol with amylene hydrate intravenously and intramuscularly, respectively. These results also are included in TABLE 2. General anesthesia was not produced in any of the cats receiving tribromoethanol. Those receiving the tribromoethanol intramuscularly did not show any effects. Those injected intravenously, however, developed a moderate to marked ataxia in 15 to 30 min. after injection. The period of generalized muscular incoordination lasted from 30 min. in 2 cats to 2½ hours in the third. These data would seem to exclude the role of spinal cord involvement and point to the potentiation of the barbiturate anesthesia by the tribromoethanol.

In a recent publication, Dwyer *et al.*[1] described the intravenous use of tribromoethanol for anesthesia. Their dosages, as calculated on the basis of a 70-kg. patient, amounted to 10.7 to 14.2 mg./kg. to "produce sleep in the average patient." These dosages are somewhat less than those employed in the cats. The dosages of 22.7 to 25.0 mg./kg. intravenously in the unanesthetized cat failed to produce sleep, but did produce definite symptoms of depression and generalized muscle incoordination. It might be assumed from these data that the human is probably somewhat more sensitive to tribromoethanol than the cat.

Effects of Tribromoethanol on Nerve Tissue

Macroscopic observations. The effects of the tribromoethanol solutions on the sciatic nerve in the present study were less severe than those for the rabbit described elsewhere. Possible explanations may be that the dose was 0.05 cc. in the present experiments, as compared with 0.1 cc. used with the rabbits, or that the solutions used with the cats were known to be stable (no color with Congo red) at the time of injection, whereas the others had not been established as negative to Congo red at the time of injection. It was established that, in the experiment using cats, the stock solution of tribromoethanol with amylene hydrate did give a blue color with Congo red, but this test was made a few days after the nerve injections were completed.

Hemorrhage, discoloration of the nerve at the site of injection, and slight adhesion to the surrounding muscle tissue were observed in varying degrees with all of the solutions except the saline. The differences in appearance at the sites of injection between the tribromoethanol solutions and the alcohol were not marked. The saline-injected nerve at 48 hours did not appear greatly different from the noninjected nerve on the opposite side. It was not possible to establish the site of injection with saline at the 7-day observation period. These findings correlated with the presence of motor paralysis in the tribromoethanol-injected animals and the complete absence of motor disturbance in the saline-injected cats.

Microscopic observations. Of the formulations studied, tribromoethanol with amylene hydrate caused the severest reaction in the sciatic nerve and the surrounding tissue. Forty-eight hours after inoculation, severe inflammation was observed in the epineurium. The surrounding connective tissue was edematous, and serofibrinous exudate, containing principally heterophiles, was attached to the adjacent muscle. Cellular inflammation was observed in and around the muscle bundles, but no damage to the muscle had occurred. The nerve components appeared to be normal. The sciatic nerve of the cat injected seven days previously with tribromoethanol and amylene hydrate was altered morphologically. The myelin sheaths and the axis cylinders were irregular and distorted in outline and often were vacuolated. This pathological change usually was observed in the parts of the nerve adjacent to the epineurium. These damaged areas contained macrophages and polyblasts. The inflammation in the epineurium had subsided, but occasional small foci of active inflammation were found. The number of fibroblasts in the epineurium was increased and an occasional giant cell was present.

There was less reaction to the injections of tribromoethanol dissolved in alcohol than to tribromoethanol and amylene hydrate. The microscopic observations differed primarily in the severity of the lesions produced by the tribromoethanol solutions rather than in the type of inflammation and nerve degeneration.

As compared to the tribromoethanol and amylene hydrate injections, the alcohol alone produced the same general kind of reaction, but the reaction was not as severe. There was little difference between the reaction following the injection of tribromoethanol and alcohol mixture and the alcohol alone.

Saline injected into the sciatic nerve caused a moderate inflammation of the epineurium at 48 hours. The 7-day injection site was completely normal except for a small increase in the numbers of fibroblasts and macrophages in the epineurium.

In no instance was there any evidence of a direct injection into the nerve fasciculi. Apparently the tip of the needle pushed the nerve bundles aside and the injections were actually made into the epineurium. Damage to the nerve itself was never observed at 48 hours. Such changes were seen only in the 7-day preparations.

From the above, it can be stated that amylene hydrate makes the tribromoethanol more irritating than does alcohol. It would be useful to try to find some other solvent for the tribromoethanol.

Summary. The following solutions were injected in a volume of 0.05 cc. into the sciatic nerve of the cat: tribromoethanol with amylene hydrate, undiluted and diluted with 95 per cent ethyl alcohol; tribromoethanol crystals, dissolved, 1 gm./cc. in 95 per cent ethanol and also diluted 1:2 with 95 per cent ethanol; and 95 per cent ethanol and sterile physiological saline solution.

Each cat injected with the tribromoethanol solutions or alcohol developed complete motor paralysis of the lower portion of the leg. The cats injected with saline did not develop paralysis.

Good to excellent X-ray delineations of the site of injection were obtained with each of the tribromoethanol solutions. None or only faint traces of radiopaque material were evident 6 hours after injection.

The duration of sodium pentobarbital anesthesia was more than doubled in those cats receiving the tribromoethanol injections.

A dose of 0.05 cc. of tribromoethanol with amylene hydrate, given either intravenously or intramuscularly, prolonged the duration of aesthesia with sodium pentobarbital in cats from less than 22 hours to 46 to 72 hours.

The same dose of tribromoethanol administered to unanesthetized cats failed to produce any obvious symptoms when given intramuscularly, but did produce evidence of generalized muscular incoordination lasting from ½ to 2½ hours when given intravenously.

Macroscopic observations of the injection sites did not reveal any obvious differences in the severity of nerve tissue damage between the tribromoethanol and the alcohol solutions. The gross pathological appearance of the site of injection with each of the solutions, except the saline, was characterized by occasional hemorrhage, discoloration of the nerve, and slight adhesion in some instances to the surrounding muscle tissue.

Microscopic examination of the injection sites demonstrated that undiluted

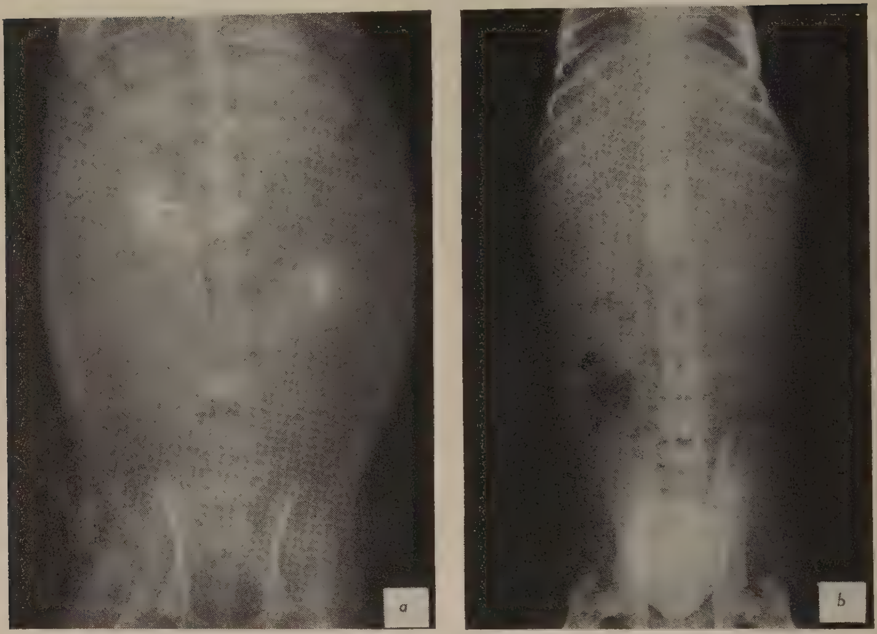

FIGURE 3. Excretory urograms with Hypaque Sodium in (*a*) the experimental rabbit and (*b*) monkey.

tribromoethanol with amylene hydrate caused the most severe reactions in the sciatic nerve and the surrounding tissues. At 48 hours severe inflammation was observed in the epineurium and, at 7 days, distinct alteration in the morphology of the sciatic nerve was apparent. A similar reaction was observed in the nerves injected with alcohol alone. Moderate inflammation was observed in the epineurium at 48 hours after injection with saline, but at 7 days the injection site appeared to be normal.

The Development of New Urographic Contrast Media

In general, the chemist can make many organic compounds that have equally good radiopacity for the diagnostic visualization of the urinary tract (FIGURES 3*a* and 3*b*). The factor that often decides whether one compound is a better urographic agent than another is toxicity. To determine the relative toxicity of these compounds, it is necessary to give animals more than one injection of the contrast media and to do detailed histological examinations of the organs and tissues. More than one species of animal should be used, for it is often possible to observe differences in the reaction of one species that are not apparent in others. The data that follow were reported previously by Hoppe *et al.*[2]

Subacute toxicity studies: the rat. Sodium diatrizoate (Hypaque Sodium,*

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* Marketed by Winthrop Laboratories, New York, N. Y.

sodium 3,5-diacetamido-2,4,6-triiodobenzoate) was injected intravenously into 10 rats in each of 3 groups. The contrast media were given in daily doses of 0.5, 2.0, and 4.0 gm./kg. for 5 consecutive days. A control group of 10 rats received, intravenously, normal saline in a volume about that injected into the group of rats on the 4.0 gm./kg. dose. Following the 5 daily injections, the rats were observed carefully for 6 more days. Four days after the last injection, hematological studies were done. The rats were sacrificed at the end of the observation period, and complete autopsies were performed. Pieces of tissue from the abdominal and thoracic viscera of the 2.0- and 4.0-gm./kg. groups were fixed in Zenker formalin, embedded in paraffin, sectioned at 6 μ, and stained by the hematoxylin and eosin method.

The rats medicated intravenously with 0.5 and 2.0 gm./kg. of sodium diatrizoate for 5 consecutive days were normal in appearance and behavior. The higher dose, 4.0 gm./kg., caused a suppression of the growth curve, and 1 rat died. The 9 survivors in this group were examined histologically, and vacuolation and displacement of the nuclei of the epithelium in the collecting tubules of the kidney were observed. No other changes were found; the glomeruli were normal.

Monkeys. Doses of 0.5, 1.0, and 2.0 gm./kg. of sodium diatrizoate (50 per cent) and sodium acetrizoate (70 per cent) were injected intravenously into groups of 2 monkeys each. The injections were made once daily with an interval of 2 days until 3 doses of the drug were given. Normal saline was administered intravenously to 2 additional monkeys as controls. Hematological studies were done before and at the end of the experiment. The monkeys were autopsied 2 days after the third injection, and pieces of the brain, spinal cord, and thoracic and abdominal viscera were studied as described in the previous section.

None of the monkeys injected with either sodium diatrizoate or sodium acetrizoate lost weight or died. Distinct generalized tensing of the monkeys was observed following each injection of sodium acetrizoate; they appeared to be in pain and often cried out. This phenomenon, reduced in intensity, was not observed in the monkeys given sodium diatrizoate until the third injection, and then only on the 1.0- and 2.0-gm./kg. dose levels. The monkeys receiving 0.5 gm./kg. were normal after each injection. Following each administration of 2.0 gm./kg. of sodium acetrizoate, 1 of the monkeys exhibited a transient tonic convulsion, cardiac arrhythmia, dyspnea, and bradycardia; it appeared to be normal in 15 to 30 min.

Upon histological examination, 4 of the 6 monkeys receiving sodium acetrizoate were observed to have cellular casts in the large collecting tubules of the kidney. None was found in the monkeys medicated with sodium diatrizoate. These casts contained large numbers of large epithelial-like cells and, often, some lymphocytes and heterophils. An increase in size of the subcapsular spaces of the glomeruli was noted at the 1.0- and 2.0-gm./kg. doses with both contrast media, but not at the 0.5-gm./kg. dose. Mottled areas observed in the lungs in all groups of monkeys on both drugs were probably related to the injections of large amounts of hypertonic solutions.

Conclusions. Comparative toxicity studies clearly demonstrated that sodium diatrizoate was well-tolerated intravenously when given in repeated daily doses as high as 4.0 gm./kg. in the rat and 2.0 gm./kg. in the monkey. No serious hematological or pathological changes were observed in the rat or monkey.

Sodium acetrizoate caused renal cellular casts to appear in the collecting tubules of 4 of the 6 injected monkeys. In addition, a serious tensing phenomenon was observed in all of the monkeys receiving sodium acetrizoate following each injection. One of the monkeys also exhibited detrimental pharmacodynamic activity.

These important observations on the part of the toxicologist and pathologist helped to establish the superiority of sodium diatrizoate in experimental animals.

Sodium Diatrizoate with and without Hyaluronidase: Radiological and Irritation Studies Following Subcutaneous and Intramuscular Injections in the Rabbit

The object of this study was to determine the effect of subcutaneous and intramuscular injections of sodium diatrizoate alone and sodium diatrizoate with hyaluronidase on the rate of absorption of the radiopaque medium, the density of the urograms, and the degree of irritation.

Fourteen adult albino rabbits, divided into 2 groups of 4 each, and one group of 6, were employed in these experiments. A 25 per cent and a 50 per cent solution of sodium diatrizoate were used in these studies. The 25 per cent solution of sodium diatrizoate was prepared immediately before use by diluting the 50 per cent preparation with sterile distilled water.

Certain phases of these studies required a solution of hyaluronidase in sodium diatrizoate. Seventy-five turbidity reducing units (TRU) of hyaluronidase were added to each cubic centimeter of a 25 per cent solution of sodium diatrizoate. The hyaluronidase used was a lyophilized, commerical preparation, Wydase.*

The experimental procedures and the results are subdivided as follows: (1) the rate of absorption of sodium diatrizoate, with and without hyaluronidase, from subcutaneous and intramuscular injection sites; (2) the density of urograms following subcutaneous and intramuscular injections of sodium diatrizoate, with and without hyaluronidase; and (3) the tissue irritation following subcutaneous and intramuscular injections of sodium diatrizoate, with and without hyaluronidase.

(1) Four rabbits, weighing approximately 3 kg. each, were divided into 2 groups of 2 rabbits each. The first group was injected subcutaneously and the second group was injected intramuscularly. Two 2-cc. injections of the test formulation were given to each rabbit, as shown in TABLE 3. Each rabbit was X-rayed immediately after medication and at 15-, 30-, and 60-min. intervals (FIGURE 4*a*, *b*, *c*). The radiograms were examined to compare the rate of absorption of sodium diatrizoate alone with the rate of absorption of sodium diatrizoate and hyaluronidase. The rabbits were sacrificed four days after the

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* Product of Wyeth Laboratories, Philadelphia, Pa.

TABLE 3

DOSAGE REGIMEN

Rabbit	25% Sodium diatrizoate dose, cc.	Hyaluronidase TRU*	Method of injection	Site of injection
1	2	150	Subcutaneous	Over right scapula
	2	150	Subcutaneous	Over left scapula
2	2		Subcutaneous	Over right scapula
	2		Subcutaneous	Over left scapula
3	2	150	Intramuscular	Right vastus lateralis
	2	150	Intramuscular	Left vastus lateralis
4	2		Intramuscular	Right vastus lateralis
	2		Intramuscular	Left vastus lateralis

* Turbidity reducing units.

administration of the radiopaque medium. The injection sites were examined macroscopically for any pathological changes, as described above in subdivision 3.

The rate of absorption of sodium diatrizoate with hyaluronidase was more rapid than was that of sodium diatrizoate alone, injected subcutaneously or intramuscularly. No radiographic shadows were observed in the subcutaneous or intramuscular injection sites after 45 min. in those rabbits receiving the hyaluronidase and sodium diatrizoate (TABLE 4). Shadows persisted for more than 60 min. following injections of sodium diatrizoate alone.

(2) Four adult albino rabbits were used. Two rabbits were injected with sodium diatrizoate alone, and 2 with sodium diatrizoate and hyaluronidase. The rabbits were starved for 48 hours and dehydrated for 24 hours prior to injection of the radiopaque medium. Each rabbit was injected with 4 cc. of a 25 per cent solution of sodium diatrizoate in 2 equal doses of 2 cc., as shown in TABLE 5. Urograms of each rabbit were taken immediately and 5, 10, 20, 40, and 80 min. after the injections. A compression bandage was applied to the abdominal region of each rabbit for 3 minutes immediately before a urogram was taken. The radiopacity of the kidney, ureter, and bladder was compared after injection of sodium diatrizoate alone with that of sodium diatrizoate with hyaluronidase. Forty-eight hours after medication the rabbits were sacrificed and the injection sites were examined macroscopically, as described below under subdivision 3.

The maximum density of the urograms was observed 40 min. after the subcutaneous and intramuscular injections of sodium diatrizoate with and without hyaluronidase. The addition of hyaluronidase to the radiopaque medium, as well as the method of injection, made no significant difference in the density of the urograms (TABLE 6).

(3) The results of the macroscopic examination of the injection sites discussed in subdivisions 1 and 2 are presented in this section. In addition, a separate study was made to determine macroscopic and microscopic intramuscular irritation. A group of six adult albino rabbits was divided into 3 groups of 2 rabbits each. The first group was injected with a 50 per cent solution of sodium diatrizoate, the second with a 25 per cent solution of so-

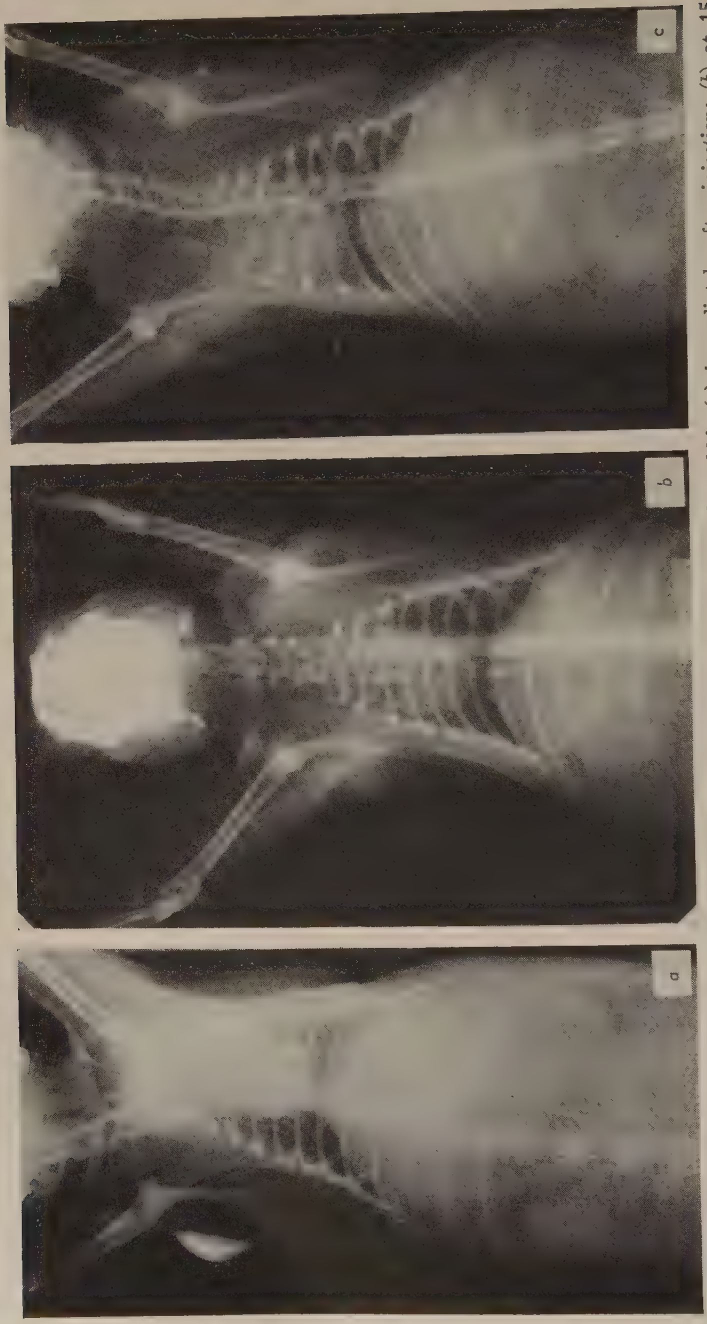

FIGURE 4. Absorption of Hypaque Sodium following subcutaneous injection in the rabbit (*a*) immediately after injection; (*b*) at 15 min. after injection (most of the Hypaque has already been absorbed); and (*c*) at 45 min. after injection absorption is complete.

TABLE 4

RADIOPACITY OF INJECTION SITES IN RABBITS

Preparation*	Total dose injected	Rabbit	Method of injection	Minutes post-injection	Density of site†	
					Right	Left
Sodium diatrizoate with hyaluronidase	4 cc. 300 TRU‡	1	Subcutaneous	0	4	4
				15	2	2
				30	2	2
				45	0	0
				60	0	0
Sodium diatrizoate	4 cc.	2	Subcutaneous	0	4	4
				15	3	3
				30	3	2
				45	3	2
				60	2	1
Sodium diatrizoate with hyaluronidase	4 cc. 300 TRU‡	3	Intramuscular	0	4	4
				15	2	2
				30	1	1
				45	0	0
				60	0	0
Sodium diatrizoate	4 cc.	4	Intramuscular	0	4	4
				15	3	3
				30	2	2
				45	1	1
				60	1	1

* Twenty-five per cent solution.
† Radiographic shadow-rating scale: 4, excellent density; 3, good; 2, fair; 1, poor; 0, none.
‡ Turbidity reducing units.

TABLE 5

DOSAGE REGIMEN

Rabbit	25% Sodium diatrizoate dose, cc.	Hyaluronidase TRU*	Method of injection	Site of injection
5	2	150	Subcutaneous	Over right scapula
	2	150	Subcutaneous	Over left scapula
6	2		Subcutaneous	Over right scapula
	2		Subcutaneous	Over left scapula
7	2	150	Intramuscular	Right vastus lateralis
	2	150	Intramuscular	Left vastus lateralis
8	2		Intramuscular	Right vastus lateralis
	2		Intramuscular	Left vastus lateralis

* Turbidity reducing units.

dium diatrizoate, and the third with a 25 per cent solution of sodium diatrizoate containing 75 TRU/cc. Each rabbit was injected intramuscularly 3 times with 1 cc. of a test formulation as follows: the first day, into the right vastus lateralis; the sixth day, into the left vastus lateralis; and the seventh day, into the right triceps. On the eighth day of the experiment the animals were sacrificed. The injection sites were observed and then fixed in Zenker formalin, embedded in paraffin, sectioned at 6 μ, and stained by the hematoxylin

Table 6
Density of Urograms in Rabbits

Preparation*	Total dose injected	Rabbit	Method of injection	Minutes postinjection	Urographic score†
Sodium diatrizoate with hyaluronidase	2 cc. 300 TRU‡	5	Subcutaneous	0	0
				5	0
				10	0
				20	20
				40	45
				80	20
Sodium diatrizoate	2 cc.	6	Subcutaneous	0	0
				5	0
				10	0
				20	20
				40	30
				80	10
Sodium diatrizoate with hyaluronidase	2 cc. 300 TRU‡	7	Intramuscular	0	0
				5	0
				10	20
				20	30
				40	45
				80	30
Sodium diatrizoate	2 cc.	8	Intramuscular	0	0
				5	0
				10	20
				20	30
				40	45
				80	30

* Twenty-five per cent solution.
† Urographic density scale: 30 to 45, fair visualization.
‡ Turbidity reducing units.

and eosin method. In this way, inflammatory reactions in the muscles of 1-, 2-, and 7-day duration were obtained for histopathological examination.

Results. There was no apparent evidence of pain, redness, or swelling at any time at the sites of injection. Macroscopic observations of 2- and 4-day injection sites from rabbits used in subdivisions 1 and 2 showed no visible evidence of subcutaneous irritation following injection with 25 per cent sodium diatrizoate solution either with or without hyaluronidase. When these solutions were administered intramuscularly, the 2-day injection sites showed mild irritation characterized by a few small, diffuse hemorrhages around the path of the injection. By the fourth day, no irritation was observed in the muscle injection sites.

Macroscopic. No difference was observed in the muscle injected with 25 per cent sodium diatrizoate, with and without hyaluronidase. The 1- and 2-day injection sites were slightly congested and a few small, diffuse hemorrhages were found at the center of injection. The 7-day injection sites appeared to be normal.

The tissue irritation observed in the 50 per cent sodium diatrizoate injection sites was similar to that described above for 25 per cent sodium diatrizoate injections except that the degree of the irritation was slightly greater. Again, by the seventh day the injection sites appeared to be normal.

Microscopic. Very mild muscular irritation resulted from the injection of sodium diatrizoate alone or with hyaluronidase. The type of tissue irritation was similar following injections of 25 per cent sodium diatrizoate, 25 per cent sodium diatrizoate with hyaluronidase, and 50 per cent sodium diatrizoate.

The degree of inflammation produced by 25 per cent sodium diatrizoate and 25 per cent sodium diatrizoate with hyaluronidase was similar, but the 50 per cent sodium diatrizoate caused a slightly greater inflammation.

Twenty-four hours. Relatively few heterophils and lymphocytes were observed in the injection sites after 24 hours. Slight edema and moderate hemorrhage were noticed in the muscles injected with 50 per cent sodium diatrizoate, but not in the muscles injected with 25 per cent sodium diatrizoate or 25 per cent sodium diatrizoate with hyaluronidase.

Forty-eight hours. At 48 hours following the injection of 25 per cent sodium diatrizoate or 25 per cent sodium diatrizoate with hyaluronidase, relatively few polyblasts and macrophages were observed. No edema or coagulative necrosis occurred. Small areas of frank hemorrhage and a moderate cellular response to inflammation were observed in the muscle injected with 50 per cent sodium diatrizoate. Coagulative necrosis was not apparent.

Seven days. Healing was well advanced by the seventh day following the injection of any of the three preparations. The injection sites at this time were small and circumscribed and could not be observed macroscopically. No new foci of cellular infiltration were found.

Conclusions. Radiograms taken at various intervals following subcutaneous or intramuscular injections of sodium diatrizoate with hyaluronidase revealed that the radiopaque substance was more rapidly absorbed from the injection sites than was sodium diatrizoate alone. However, the addition of the hyaluronidase to the sodium diatrizoate solution had no significant effect on the density of the urograms. Maximum density of the urograms was observed 40 min. after either subcutaneous or intramuscular injections.

In general, a low degree of intramuscular irritation was observed following injections of sodium diatrizoate with or without hyaluronidase. Many of the injection sites were normal in appearance, but moderate congestion and diffuse hemorrhage were observed in a few instances.

SUMMARY

This presentation gives the details of some experiments in which the toxicologist and pathologist contributed to the successful understanding and use of various X-ray contrast media. As new X-ray contrast media are developed, these scientists will be called upon to devise different experimental approaches that will aid in the selection of the best compounds.

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HEAVY-METAL CHELATES AND CESIUM SALTS FOR CONTRAST RADIOGRAPHY

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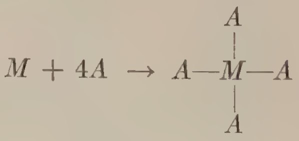
The search for the ideal radiographic contrast medium continues unabated. To be sure, there have been many valuable contributions to contrast radiography of special organs: for example, air and other gases for the study of the central nervous system and various organic iodine derivatives for such techniques as cholecystography and pyelography. Nevertheless, the ideal medium for general radiographic use has successfully eluded discovery thus far. There is more or less general agreement about the basic characteristics desirable in such a medium: (1) satisfactory radiopacity (primarily a function of the atomic number of the element in the medium, but also related to concentration), (2) stability, (3) pharmacological inertness, and (4) minimal toxicity and sensitizing properties.

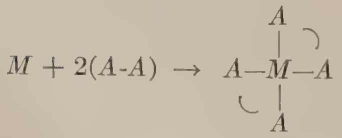
In 1952, while studying chelation in relation to the detoxification of heavy metals, we became interested in the application of this principle to contrast radiography. On theoretical grounds, at least, it seemed that a heavy metal chelate might satisfy all of the criteria of the so-called ideal radiographic medium. Consequently, a long-term investigation of these compounds was initiated.

The term chelation, derived from the Greek χηλη (claw), signifies the tenacious grip that certain organic compounds have on metals, particularly heavy metals and the alkaline-earth group. When a metallic ion combines with one of these organic compounds, the resulting substance is a metal complex. If the substance combining with the metal has two or more donor groups, so that a ring compound is formed, the latter is termed a chelate. Simple diagrammatic illustrations of complex formation and chelation may be schematized as follows:



$$M + 4A \rightarrow \begin{array}{c} A \\ | \\ A\text{—}M\text{—}A \\ | \\ A \end{array}$$

metal complex



$$M + 2(A\text{-}A) \rightarrow \begin{array}{c} A \\ | \\ A\text{—}M\text{—}A \\ | \\ A \end{array}$$

metal chelate

where M is a metallic ion, A the complexing agent, and A-A the chelating agent.

Chelates are stable, water-soluble ring compounds in which the metal is so firmly bound in the nonionic form that it loses its usual characteristic chemical

TABLE 1

STABILITY CONSTANTS OF EDTA COMPLEXES

Element	Log K	Element	Log K
Na^+	1.66	Co^{++}	16.10
La^+	2.79	Cd^{++}	16.48
Ba^{++}	7.76	Zn^{++}	16.58
Sr^{++}	8.63	Pb^{++}	18.2
Mg^{++}	8.69	Cu^{++}	18.38
Ca^{++}	10.59	Ni^{++}	18.45
Mn^{++}	13.47	Cr^{+++}	24
Fe^{++}	14.42	Fe^{+++}	25
La^{+++}	15.4		

properties. Ethylenediaminetetraacetic acid (EDTA), a stable, insoluble, synthetic acid, is probably the most familiar exogenous biological chelating agent. If the disodium monocalcium salt of EDTA is prepared, it does not give any of the characteristic tests for ionic calcium: that is, it does not form a precipitate with phosphate, carbonate, hydroxide, or even oxalate. This can mean only that the calcium in the compound no longer exists in the free ionic state. Actually, it is bound in the form of a chemically inert, complex anion, so that it no longer possesses the characteristic cationic properties of calcium.

Because EDTA is a tetrabasic acid (that is, it has four replaceable hydrogen atoms), the addition of NaOH results in the progressive formation of mono-, di-, tri-, and tetrasodium salts. Although most of the metallic elements are capable of forming chelates, they vary a good deal in their ability to combine with EDTA. This is well demonstrated in data on stability constants (K) of the various EDTA complexes[1] (TABLE 1).

The constant K indicates the ratio of metallic chelate in equilibrium with "free" metallic ions. The greater the value of log K, the stronger the tendency to chelate formation. Likewise, the greater the log K value, the more stable the chelate. It is also apparent from the table that the transitional elements are good complexers and that the higher oxidation state makes for stronger complexes.

In addition to the atomic weight of the cation, there are a number of other factors that affect the ionic equilibrium in chelate formation: for example, H^+, the addition of neutral electrolytes, and temperature. In general, an increase in H^+ concentration, the addition of neutral electrolytes (for example, NaCl and KCl), and a rise in temperature all tend to decrease complex formation and metal chelate stability. However, for practical purposes, the effect of temperature is negligible.

The portion of this report concerned with chelates will deal principally with lead-sodium EDTA and, to a lesser extent, with preliminary studies on monolead trisodium diethylenetriamine pentaacetate and monolead disodium, 2-1, diaminocyclohexane tetraacetate.

Methods

The monolead disodium salt of EDTA is prepared by adding a concentrated solution of the tetrasodium salt to an equivalent solution of lead chloride.

Upon cooling, the lead disodium salt crystallizes out in the form of an odorless, white powder. The material used in this study* was a clear, stable, colorless 34 per cent solution with a *p*H of 7.0 to 7.2. The lead is so firmly bound by the EDTA that the addition of K_2CrO_4 *in vitro* fails to precipitate yellow $PbCrO_4$. Likewise, spectroscopic analysis fails to demonstrate the characteristic band of Pb^{++}, thus confirming the relative absence of "free" lead ions in the preparation. The 34 per cent solution was utilized both in its original form and after dilution to 11 and 20 per cent solutions with sterile distilled water or 10 per cent calcium disodium versenate.

These materials were given to cats, rabbits, guinea pigs, and dogs orally, intraperitoneally, intramuscularly, and intravenously. The latter injections were made into the femoral vein in cats, guinea pigs, and dogs, and into the marginal ear vein in rabbits.

Pharmacology

Acute intravenous toxicity. In the present study, the acute intravenous LD_{50} of 34 per cent lead disodium versenate in guinea pigs and rabbits was determined to be 800 mg./kg. Similar data were reported by Bauer and his associates,[2] who found the acute intravenous toxicity in rabbits to be 1000 mg./kg. It is important to note that there is a considerable species variability in toxicity. For example, we have injected cats with as much as 3 gm./kg. intravenously without overt toxicity. This increased tolerance is probably also true of mice and dogs. Thus, Clark and Tomich[3] determined that the acute intravenous LD_{50} varied from 3.5 to 4.5 gm./kg. in 2 different strains of mice, while Cannon[4] reported that intravenous injection of 4.6 gm. of lead chelate in dogs produced no obvious toxic manifestations.

Single, large, rapid injections (>800 mg./kg.) of lead disodium versenate intravenously into rabbits and guinea pigs resulted uniformly in increased irritability, generalized convulsions, respiratory failure, and rapid death. Because death was so prompt, no significant findings were noted at necropsy. However, the type of death suggested central nervous system irritation with respiratory center depression. Several rabbits that received smaller doses (300 to 500 mg./kg.) developed gross hematuria. Histological study of the tissues of the animals in the 2 groups of rabbits that died or were sacrificed showed hepatorenal damage.[5]

Acute intraperitoneal toxicity. Although Bauer *et al.*[2] found the acute intraperitoneal LD_{50} for rabbits to be 350 mg./kg., in a group of 6 rabbits, in our study, the acute intraperitoneal and intravenous toxicities were quite similar.

Acute intramuscular toxicity. Two rabbits were injected intramuscularly with 2 gm./kg. of 34 per cent lead disodium versenate, without immediate obvious toxic manifestations. However, both rabbits died within 18 hours after injection, and both exhibited gross hematuria, which commenced several hours after injection. Some absorption of the injected material was detected on the roentgenograms at 30 min.; at 45 min., there was opacification of the bladder, but not of the kidneys.

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* Lead disodium versenate, furnished by The Bersworth Chemical Co., Framingham, Mass.

Acute and chronic oral toxicity. We fed as much as 1 gm./kg. of lead disodium versenate (34 per cent solution) orally to cats as an acute study, with no evidence of toxicity. Clark and Tomich[3] administered oral doses of 100 and 500 mg./kg. to a small group of rats, also with no overt, demonstrable toxicity; all were sacrificed after 2 weeks. Except for slight renal damage in the animals that received 500 mg./kg., the remaining organs were entirely negative. The liver, kidneys, gastrointestinal tract, spleen, femur, and blood from a rat at each dose level were assayed for lead with negative findings.

The Bersworth laboratories reported chronic oral toxicity studies in groups of 6 rats fed 65 mg./100 ml., 91 mg./100 ml., and 150 mg./100 ml. of lead chelate.[6] The surviving animals were sacrificed after 21 months, 1 animal of the group receiving the highest dosage, 3 receiving the intermediate dosage, and 5 receiving the lowest dosage. Necropsy demonstrated congestion of the liver; pale, swollen kidneys; and hemorrhagic lesions of the small bowel.

An attempt was made to decrease the toxicity of lead disodium versenate by pretreating the animals with calcium disodium versenate. The rationale of this effort was an attempt to saturate with the less toxic calcium chelate the physiological systems competing for chelates, so that lead chelate, introduced afterward, might pass through unchanged. In these experiments, rabbits were pretreated by preliminary intravenous injection of 500 mg./kg. of calcium disodium versenate. Two hours later, the rabbits received an intravenous injection of 34 per cent lead disodium versenate that had been diluted by the addition of a solution containing 200 mg./kg. of calcium disodium versenate. However, no significant diminution in toxicity was noted when equivalent amounts of lead disodium versenate were employed.

Excretion studies were carried out on rabbits, cats, and guinea pigs after parenteral injection of lead disodium versenate. These studies demonstrated that the principal route of excretion was the kidney. Between 70 and 90 per cent of the injected lead was recovered in the urine during the first 24 to 48 hours. The remainder was excreted in the feces, except for a small amount deposited in the body tissues.

After oral ingestion, a substantial amount of the lead chelate is absorbed from the intestinal mucosal surface, carried to the liver by the portal venous system, and subsequently excreted in the urine. This train of events can be visualized roentgenologically as the urinary bladder becomes progressively opacified after oral ingestion of lead chelate.

Sapeika[7] reported transient hypotension after the intravenous injection of 1.0 ml./kg. of 50 per cent lead chelate in cats. Elevated T waves were noted in the electrocardiograms used to monitor these injections. Sapeika suggested that the myocardial changes could be the result of hyperkalemia due to a transient imbalance of the Ca-K ratio.

Contrary to some reports in the literature,[8-10] our present studies, which are corroborated by Tjernberg[11] and by the work of Clark and Tomich,[3] indicate that lead disodium versenate is toxic *in vivo* in spite of considerable species variability. It is also evident that, although this compound contains little "free" ionic lead *in vitro*, the situation changes upon introduction of the lead disodium versenate into the body. Under the latter circumstances, the lead

EDTA complex undergoes dissociation, with the release of free lead ions, as evidenced by the prompt onset of toxic reactions after intravenous injection. There is probably a brisk physiological competition between naturally occurring chelating substances for various cations. Thus, ions may compete either with EDTA for the lead or for the EDTA itself. For example, when the lead chelate dissociates *in vivo* in the presence of Cl ions, the Pb combines with the Cl to form $PbCl_2$ and higher complexes, resulting in progressive dissociation of EDTA. Dissociation of the lead EDTA complex is also favored by those metals in the body (for example, Cu^{++} and Fe^{+++}) that form EDTA complexes as strong as or stronger than the lead EDTA complex, since a metal's affinity for a chelating agent parallels roughly its electronegativity sequence.

Because 5-carbon chelates and cyclic chelate compounds are stronger complexing agents than EDTA, studies are now under way with monolead trisodium diethylenetriamine pentaacetate and with monolead disodium 1,2-diaminocyclohexane tetraacetate, both in the form of 25 per cent solutions. To date, these studies are quite preliminary and incomplete. However, it does not appear that these compounds are significantly less toxic than lead disodium versenate. In addition, as might be anticipated, the resulting radiopacification from the 25 per cent solutions is less satisfactory than that with the 34 per cent lead versenate.

Radiographic Findings

Shortly after (within 5 min.) the intravenous injection of 34 per cent lead disodium versenate, brilliant nephrograms of the kidneys are obtained—an effect that persists to some degree for approximately 20 min. Within 10 min. after injection, early opacification of the renal pelvic and calyceal structures can be noted, with maximal visualization of the pelves and calices occurring within 30 to 45 min. Often one can see a combined nephrogram-pyelogram on the 15-min. film. This, of course, would be invaluable in the early diagnosis of renal parenchymal lesions, particularly small neoplasms. Opacification of the urinary bladder occurs to some degree as early as 15 min. after intravenous injection.

Lead disodium versenate also produces excellent contrast visualization of the cardiovascular system, liver, and spleen. This is perhaps most dramatically demonstrated in the films exposed immediately after intravenous injection of the rabbits that died during the acute-toxicity studies.

The oral ingestion of lead disodium versenate produces good visualization of the gastrointestinal tract. Since the lead chelate is a solution and not a suspension, it is readily miscible with the gastrointestinal contents, thus producing a uniform, homogeneous shadow without flocculation. Unfortunately, some of the material is absorbed from the intestinal tract into the blood stream and, in turn, is excreted by the kidneys. Sapeika reported the occurrence of black feces after feeding lead versenate orally to a patient. We and Clark and Tomich have found this to be due to the fact that lead EDTA is decomposed by sulfides, with the resultant formation of a black precipitate.

Cesium Chloride as a Radiopaque Agent

Our previous experimental studies suggest that an element with an atomic number in the minimal range of 50 is necessary for satisfactory radiopacification in man.[12, 13] This is in keeping with the following equation:[14]

$$\mu = k\lambda^3Z^4 + 0.2$$

where μ is the absorption coefficient; k, a constant; λ, the wave length of the radiation; Z, the atomic number of the element and 0.2, the coefficient of scattering, which varies only slightly with the wave length.

In the voltage range commonly employed in diagnostic radiography in man, absorption is due principally to the photoelectric effect. Since absorption is proportional to the fourth power of Z, obviously it increases markedly for the heavier elements. The tube voltage is important because absorption is also proportional to the cube of the wave length. In the 70 to 90 kvp range used for diagnostic roentgen studies, a large part of the radiation in the heterochromatic beam falls where the elements with lower atomic numbers—for example, Br (35) and Zr (40)—absorb but little. Conversely, at lower kilovoltages (30 to 40 kvp, used for radiography of small animals and of solutions in test tubes) a relatively greater quantity of radiation may fall in the K-absorption peak of elements with atomic numbers lower than 50. This explains the apparent paradoxical finding (at lower kilovoltages) of insignificant differential radiopacity between 2 elements with a marked difference in atomic number.

Various soluble cesium salts (for example, cesium chloride and cesium bitartrate) were selected for study, because cesium has an atomic number of 55 forms soluble salts quite readily, and resembles potassium biochemically.

Materials and Pharmacology

When injected intravenously, CsCl is rapidly excreted, principally by the kidneys (80 to 85 per cent) and, to a lesser extent (15 per cent), by the intestinal tract. Acute intravenous toxicity studies in rabbits and dogs showed that 700 mg. of a 30 per cent solution of CsCl produced hyperactive reflexes and increased masticatory movements, but no other toxic manifestations. The intravenous injection of 1500 mg. frequently resulted in extrasystoles and diarrhea. However, the intravenous administration of 3000 mg. of this solution invariably produced increased irritability, generalized convulsions, gasping respirations, apnea, and cardiac standstill. Death invariably occurred within a few minutes after the latter dosage.[15] This is in keeping with Hanford's data[16] which, although demonstrating some species variability, showed that parenteral CsCl was toxic alike to frogs, rabbits, cats, and dogs. In these studies, the subcutaneous injection of 0.5 to 2.0 gm. of CsCl per kilogram of body weight produced diarrhea, vomiting, progressive paralysis, and death; the intravenous injection of 0.75 gm. of CsCl per kilogram of body weight resulted in cardiac standstill.

These findings are somewhat at variance with the data of Cochrane and his

TABLE 2

DATA ON TOXICITY OF CESIUM SALTS*

Compound	LD_{50} of compound	LD_{50} of metal, mg./kg.
CsCl	1500	1118
CsBr	1400	874
CsI	1400	715
$CsNO_3$	1200	817
CsOH	100	89

* After Cochrane *et al.*[17]

co-workers,[17] which suggest that most cesium salts (with the exception of CsOH) are relatively nontoxic after intraperitoneal injection (TABLE 2).

Radiographic Findings

This portion of the report is concerned principally with the use of cesium chloride and cesium bitartrate for bronchography and hysterosalpingography. Dogs were used entirely for this part of the study.

Prior to bronchography, the animals were anesthetized with veterinary Nembutal given intravenously. A rubber catheter was placed in the trachea and 10 to 20 cc. of 30 per cent cesium chloride or cesium bitartrate was injected through the catheter without any obvious toxic reactions. In a group of 12 test animals, the radiopacity was good. However, the cesium salts tended to alveolarize quite rapidly and were also completely absorbed from the bronchopulmonary tree within 5 min. This made conventional radiography impossible, but good spot films were easy to obtain. In an effort to decrease the tendency to pass out into the alveoli and also to delay absorption, various thickening agents were added: 3 to 8 per cent sodium carboxymethyl cellulose and 3 to 6 per cent polyvinyl pyrrolidone. Although the thickened solutions tended to remain in the larger bronchi and were absorbed somewhat more slowly (8 to 15 min.), the increased viscosity made injection much more difficult.

After further animal studies, left upper lobe segmental bronchograms were done in 2 patients with bronchogenic carcinoma, using 30 per cent CsCl thickened with 3 per cent sodium carboxymethyl cellulose. Following preliminary sedation with Seconal and topical anesthesia (1 per cent Pontocaine), CsCl was instilled through an intratracheal catheter. In both cases, the radiopacity was quite satisfactory, but the CsCl was absorbed from the tracheobronchial tree within 3 min. In addition, both patients complained of fairly severe left upper chest pain as soon as the CsCl was injected.

At operation, the day following bronchography, both patients were found to have wet left lungs. This is in keeping with our other experimental studies that demonstrate that all hypertonic aqueous solutions produce hyperemia and varying degrees of epithelial damage when applied to respiratory epithelium.

Prior to hysterosalpingography, 6 dogs were anesthetized with veterinary Nembutal intravenously. Ten cc. of 30 per cent CsCl was injected through the cervical *os*, and roentgenograms were made. Again the radiopacity was good and no obvious toxicity was noted in this group of animals. The CsCl was absorbed fairly rapidly from the peritoneal cavity (20 to 30 min.).

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CHELATES AS POSSIBLE CONTRAST MEDIA

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While the marked X-ray opacity characteristic of the heavy metals would suggest the obvious utility of these elements as possible contrast media, this use has not yet been realized because of the profound toxicity that metal ions exert on living systems. The development of new types of metal-binding agents has reopened study of this field in the last few years.

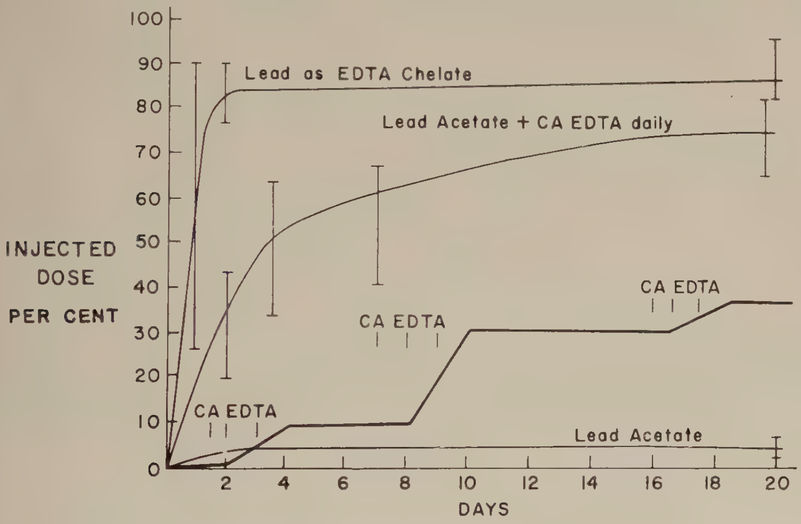
There are many examples of the fact that the binding of metals by organic molecules may profoundly alter their absorption, distribution, excretion, and metabolic function *in vivo*. It is thus not unexpected that metal toxicity, which is a summed measure of all of these characteristics, may be strikingly increased or decreased by binding with organic ligands. The nature of the alteration in toxicity is a variable function of the particular metal, the organic binding agent, the route of administration, and the species under investigation.

The metal chelating agent ethylenediaminetetraacetic acid (EDTA) has been of special interest because of its unusual physical, chemical, and biological properties. For many metals, EDTA chelation brings about a profound decrease in metal toxicity as determined by parenteral administration in animals.[1] TABLE 1 summarizes significant findings in a study of the comparative acute toxicity of inorganic salts and metal EDTA chelates administered by intraperitoneal injection in the rat. It is of interest to note that the degree of detoxification is highly variable, depending on the metal under consideration. While the nickel, cobalt, and calcium EDTA chelates show marked decrease in toxicity compared to the metal ions, the effect is less significant for mercury and chromium. The threefold detoxification of lead (determined in acute-toxicity studies) that could be achieved by EDTA chelation led to the subsequent development of this agent as a means for therapy in lead poisoning.[2, 3] The effectiveness of the EDTA-chelation treatment of lead poisoning rests on the facts that chelation with lead can take place under the conditions present *in vivo*; that lead may be removed in this way from its site of binding *in vivo*; and that the lead EDTA chelate formed is nonmetabolized, highly water-soluble, and readily excreted through the urinary system. These aspects of the metabolic behavior of the lead EDTA chelate, coupled with the marked X-ray opacity of lead, caused us to make an examination of the potential of the agent for contrast urography.[4] Despite the technically interesting contrast results that were obtained, the more intensive investigation of the degree of tissue-lead deposition following administration of the lead EDTA chelate led us to the conclusion that clinical studies of the agent were not indicated. Such reports by others have appeared in the literature.[5-7] It would appear that the weight of present opinion does not favor clinical study of lead EDTA as a contrast agent.[8-11]

Because they illustrate a major problem in the possible application of metal

TABLE 1
ACUTE TOXICITY OF CATIONS AND THEIR EDTA CHELATES IN RATS
Intraperitoneal LD_{50} (7-day mortality)

Compound	Cation, mg./kg.	LD_{50} of chelate, mg.
Calcium (chloride)	65 ± 12	816 ± 38
Nickel (chloride)	5.9 ± 1.4	600 ± 22
Cobalt (acetate)	12 ± 2.1	212 ± 14
Copper (sulfate)	13.2 ± 3.6	40 ± 6
Mercury (chloride)	8 ± 2.1	10 ± 3.6
Chromic (acetate)	65 ± 7.7	74 ± 11
Lead (acetate)	540	1825 ± 128



CA EDTA dose, 1500 mg./kg. I.P.
Lead as acetate, 10 mg./kg. I.V.

FIGURE 1. Urinary excretion of lead in rabbits.

chelates as contrast media, a recapitulation of our studies on the metabolism and distribution of injected lead EDTA is of interest. The essential question to be answered concerns the quantitative fate and tissue distribution of the administered metal. Following intravenous administration to rabbits of lead as the EDTA chelate at a dose level of 10 mg./kg., the lead appears in the urine to the extent of 85 to 89 per cent of the injected dose within 2 days (FIGURE 1). It may be noted that the urinary excretion of lead is rapid and of short duration. While the individual range of excretion is wide for rabbits in the first 24-hour period (possibly reflecting variability in kidney function), the range for the group has narrowed considerably by the end of the 2-day collection period. While the urinary excretion of lead is at a high level it may be noted that some 10 to 15 per cent of the injected lead has been retained in the animal. The rate of decrease of the body-lead burden after 2 days is slow and consistent with the concept that the retained lead is fixed in bone, tissue, or both in the nonchelated form. In this state it would follow the well-known pattern of slow elimination of lead from the body. In contrast to the chelated lead, lead injected as the acetate resulted in low levels of urinary excretion. An average of about 5 per cent of the injected lead had been excreted in the urine at the end of the 20-day experimental period. The effect of calcium EDTA in inducing the urinary excretion of lead after administration to rabbits as the acetate is evident in FIGURE 1. Vigorous daily therapy instituted at the time of administration of the lead compound resulted in a large decrease in the body burden of lead with excretion by way of the urinary system. Urinary excretion of the lead is explicable only in terms of the conversion of the tissue- and bone-fixed lead to the chelated form, which can be handled by the renal pathway. It is also of interest that the delayed and intermittent administration of the calcium EDTA was considerably less effective in causing elimination of body-deposited metal. This points up certain facets of metal metabolism that are basic considerations in their possible use *in vivo* and of primary significance in treatment of metal toxicity. Once a bone-seeking metal has been fixed and has been made poorly available in bone by the normal processes of bone recrystallization and remodeling, the task of removal from the organism is complex and difficult. Since the fecal excretion of lead following intravenous administration of lead EDTA is less than 1 to 2 per cent of the injected dose, one may inquire as to the fate of the lead retained in the animal. Analysis of the liver indicates that the major portion of the residual lead is deposited in this organ (FIGURE 2). While the liver lead is only 5 per cent of the injected dosage, this represents almost 50 per cent of the residual lead in the animal in the early period following administration of the compound. The contrast of liver-lead content following administration of lead acetate and of liver lead following chelate treatment is note-

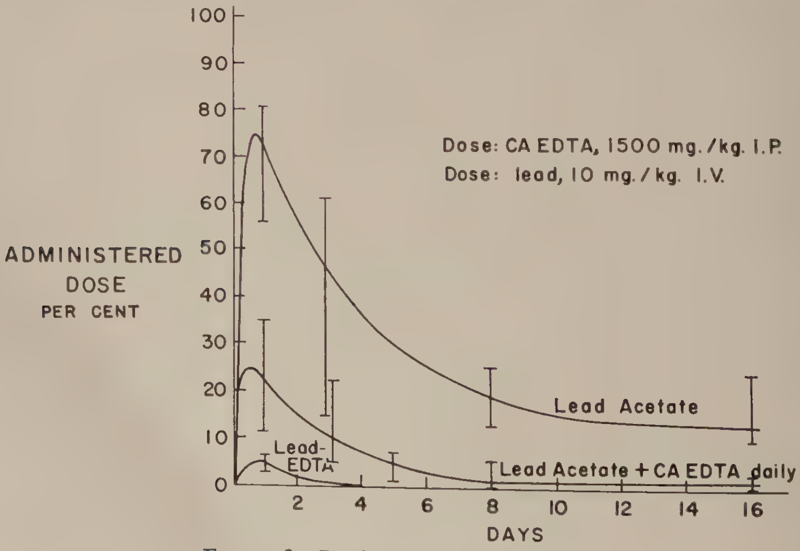


FIGURE 2. Lead content of rabbit liver.

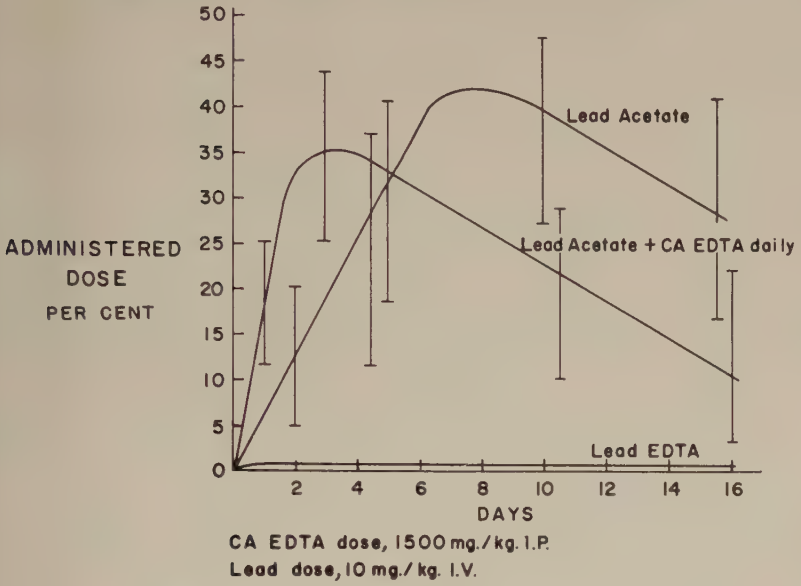


FIGURE 3. Lead content of rabbit bone marrow.

worthy. As subsequent clinical experience has clearly demonstrated, lead may be mobilized and removed from soft tissue deposits by suitable chelate administration.

The bone-marrow lead following lead EDTA administration (FIGURE 3) is low in gross amount, but again, it nevertheless represents almost 20 per cent of the lead retained in the animal. Again one may note the marked effect of chelation on marrow deposition of the metal. The time of peak deposition of the metal in marrow has been accelerated by chelate treatment while, simultaneously, the mobilized lead has in part cleared through the kidney by urinary excretion. The net effect of chelate treatment of tissue lead has been to speed up the process of tissue redistribution and excretion by bypassing the usual metal transport systems operative *in vivo*. It is of interest that serial study of lead in the hard bone shows a characteristic pattern of build-up of lead content.

The values for the total lead content of the spleen were so low (compared to the injected dose of chelated lead) and the variation in relative spleen size in the animals so large that comparison based on lead content of the entire organ has a marked uncertainty. A better indication of the lead content of the spleen has been obtained by a consideration of the concentration of lead per gram of tissue of the organ. TABLE 2 records the data for the period up to the sixth day after lead administration. The animals injected with the lead chelate showed the presence of no more than trace quantities of lead in the spleen. In contrast, one may see from the results of the 5-day observation period that a high lead concentration in the spleen in the first day after intravenous lead acetate administration was followed by a decline to about one third to one half the initial level during the next 4-day period. The animals treated with cal-

Table 2

Average Lead Content of Rabbit Spleen*

Day	Lead acetate	Lead acetate, treated	Lead EDTA
1	145 ± 21	192 ± 29	Trace
3	51 ± 28	19 ± 7	Trace
5	73 ± 15	22 ± 9	Trace

* In micrograms per gram.

Table 3

Average Lead Content* of Rabbit Gastrointestinal Tract

Sample	Lead acetate			EDTA-treated lead acetate			Lead EDTA		
	1st day	3rd Day	5th Day	1st Day	3rd Day	5th Day	1st Day	3rd Day	5th Day
Stomach tissue	None	5.0	None	None	None	None		None	
Stomach contents	2.5	17.2	18.0	None	None	None		None	
Small intestine tissue	None	2.7	None	None	None	None		None	
Small intestine contents	None	8.6	None	None	None	None		None	
Large intestine tissue	7.5	3.0	None	None	None	None		None	
Large intestine contents	2.0	34.5	35	None	None	10.0†	None		Trace

* In micrograms per gram.

† Single animal had 30.0 μg./gm. of lead; lead was absent in the samples of the 2 other members of the group.

cium EDTA exhibit a higher initial lead concentration in spleen, but show a more precipitous drop in lead to a lower concentration level at the end of the fifth day.

The results of the analysis of the lead contents of the gastrointestinal tracts of rabbits given intravenous lead EDTA, lead acetate, and the same lead acetate dosage (10 mg./kg.) of lead followed by calcium EDTA therapy are listed in TABLE 3 for the first 5-day period following lead administration. The results given are the averages of the analytical values of samples from 3 rabbits. The large individual variation from the calculated average value requires that the figures be treated with great caution. Some general trends may be gleaned, however, from these results. It is clear that, following the administration of intravenous lead acetate, the lead level in the G.I. tract builds up in the first days and then undergoes gradual decline. Of significance is the fact that lead was found in the stomach contents. This result argues the possibility of coprophagy for these animals. It had been believed that the design of the metabolic cage was such as to eliminate or at least minimize this factor, but any other source of the origin of lead in the stomach contents is not readily conceivable. While intestinal lead after intravenous administration is explicable on the basis of the known route of biliary excretion of lead, the relatively high levels of the metal demonstrated in the present study suggest that, in this case, the origin of the intestinal lead was the normal passage from stomach contents. The animals treated with calcium EDTA show a general absence of lead in the G.I.

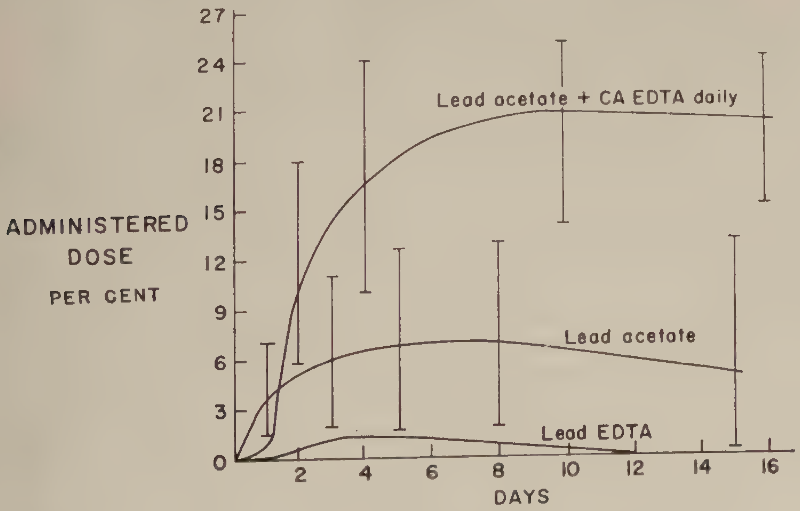
tract. Similarly, the administration of lead EDTA chelate was not followed by excretion of lead into the tract.

Lead Content of Kidney, Heart, Lungs, Muscle, and Blood

Serial analysis of the lead content of the tissues of the animals in the three groups studied yielded a large body of data difficult to evaluate because of wide individual variations. It may be generally stated that the kidney tissue showed the presence of lead in all three experimental groups. The concentration of lead was highest for those animals given intravenous lead as acetate. Lead was generally absent from heart tissue. The other soft tissues, such as lung and muscle, showed variable quantities of lead that were usually highest in the lead acetate–treated rabbits, lower in the calcium EDTA–treated group, and absent in the lead EDTA chelate group. Blood-lead levels in the period of one to five days were highest in the treated group, lower in the lead acetate–injected animals, and absent in the lead EDTA injected animals.

Lead Content of the Hard Bone

Serial analysis of the femurs of the rabbits studied yielded the results plotted in FIGURE 4. The analytical values for the femur have been converted to those for skeletal bone by the usual factor. Injection of lead as the acetate was followed by rapid deposition of lead in the hard bone. Peak levels were reached in 6 to 8 days; the subsequent decrease in bone lead was very gradual. Treatment with calcium EDTA resulted in an increased deposition of lead in the bone. The peak lead levels in the treated rabbits were reached in about 8 days and were more than twice the levels attained by the untreated group. The



CA EDTA dose, 1500 mg./kg. I.P.
Lead dose, 10 mg./kg. I.V.

FIGURE 4. Lead content of rabbit bone.

rate of subsequent decline following peak bone-lead levels was about the same in both these groups. Following administration of the lead in the same dosage (10 mg./kg.) as EDTA chelate, the bone-lead level was the lowest of the 3 experimental groups. Peak concentrations of about 2 per cent (average) of the injected lead dose were reached in about 4 days. By the end of 12 days, no more than trace quantities of lead were to be found. The rate of decline of bone-lead concentration was no faster in this experimental group than in the first 2.

Total Recovery of Injected Lead

From the lead concentration in the excreta and in individual tissue samples and by the utilization of the usual factors, the recovery of the injected dose of lead was calculated for each of the rabbits included in the above tabulations. The range of recovery was between 82 and 107 per cent of the injected dose of lead.

The pattern of distribution and excretion of lead given as the EDTA chelate is strikingly different from that of lead in other forms. However, despite the high urinary excretion of the metal and the relatively low levels of tissue distribution, it must be pointed out that, for the very large quantities of metal that would be required for contrast purposes, the probable retention is higher than can be tolerated with equanimity. When one considers that an estimated body burden of 50 mg. of lead would constitute severe lead poisoning, the possibility of retention of 10 per cent of the 5000 mg. of lead required for urography provides small comfort. A case of potentially severe lead poisoning is too high a price to pay for a technically good film of the genitourinary tract. What are the possibilities that other metals and other chelating agents may provide a more satisfactory solution of this problem? A beginning survey of these possibilities has been carried out by study of a series of chelating compounds of varied structure in combination with a variety of metals of satisfactory opacity characteristics.

The testing *in vitro* of the X-ray opacity of the various compounds was done in the following way. A board of relatively nonopaque (to X rays) material was equipped with small wells, all of the same dimension, to hold the test solutions (FIGURE 5). Equal amounts of the different solutions were placed in the wells. The board was X rayed, using standard technical factors and a standard darkroom technique. In an attempt to be as objective as possible in establishing the opacity of the test solutions, the reading of the densities was first done with a densitometer. Soon, however, it was evident that the direct estimation obtained by naked-eye evaluation of the densities was sufficiently accurate for our purposes. The concentration of the different compounds was always expressed as concentration of the metal present in the solution. Three different series of experiments *in vitro* were carried out. In a first series equal amounts of different chelated compounds, each at a different concentration, were placed in the wells to be compared with commonly used clinical iodinated contrast material. In these experiments the concentration chosen was the one compatible with the optimal stability of the solution of the chelated compound.

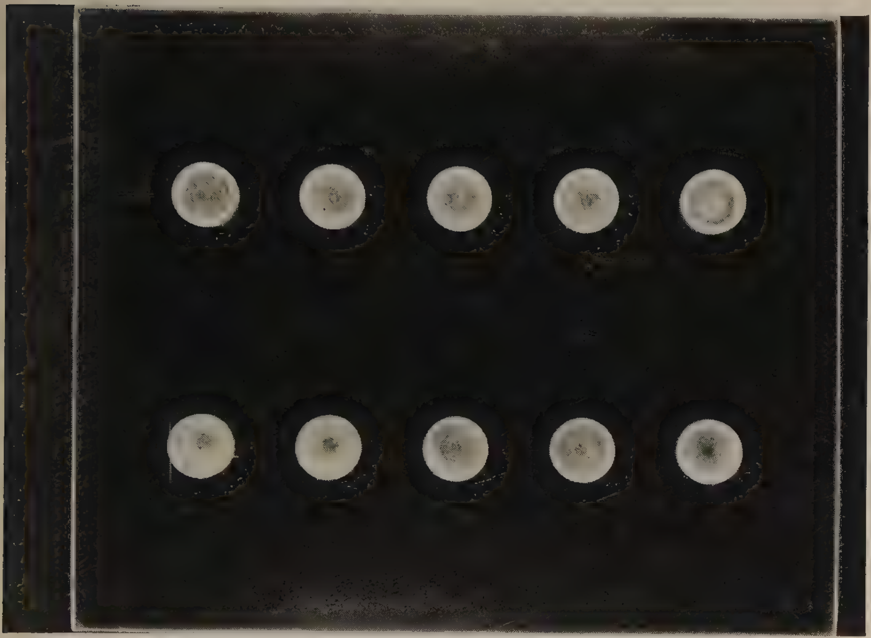


FIGURE 5. Board and wells for testing opacity of solutions.

Five iodinated radiographic contrast media* were used for comparison. FIGURE 6 shows an example of a comparative-opacity study of standard contrast media and different chelated compounds in different concentrations.

In a second series of experiments *in vitro*, solutions in different concentration of the same chelated compound were tested in order to determine the concentration providing optimal opacity. FIGURE 7 shows an example of such a type of experiment, in which 5 solutions with different concentration of lead EDTA, and 4 solutions with varying concentration of cadmium EDTA were tested.

In a third series of experiments, solutions of chelated compounds of equal metal concentration were tested. FIGURE 8 shows an experiment of this type in which five 7 per cent solutions of different chelated compounds were evaluated.

TABLE 4 is a list of the chelated compounds tested, in their different concentrations. The testing *in vitro* was done for all the listed compounds, while only some were tested *in vivo*. TABLE 5 gives the complete chemical names of the chelated compounds with their abbreviations.

These three series of experiments *in vitro* demonstrate, as could have been

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* The media used and their manufacturers are: Diodrast 35 per cent, Skiodan 30 per cent, and Hypaque 50 per cent, all products of Winthrop Laboratories, New York, N. Y.; Urokon 70 per cent, Mallinckrodt Chemical Works, St. Louis, Mo.; and Pantopaque, Lafayette Pharmacal Inc., Lafayette, Ind.

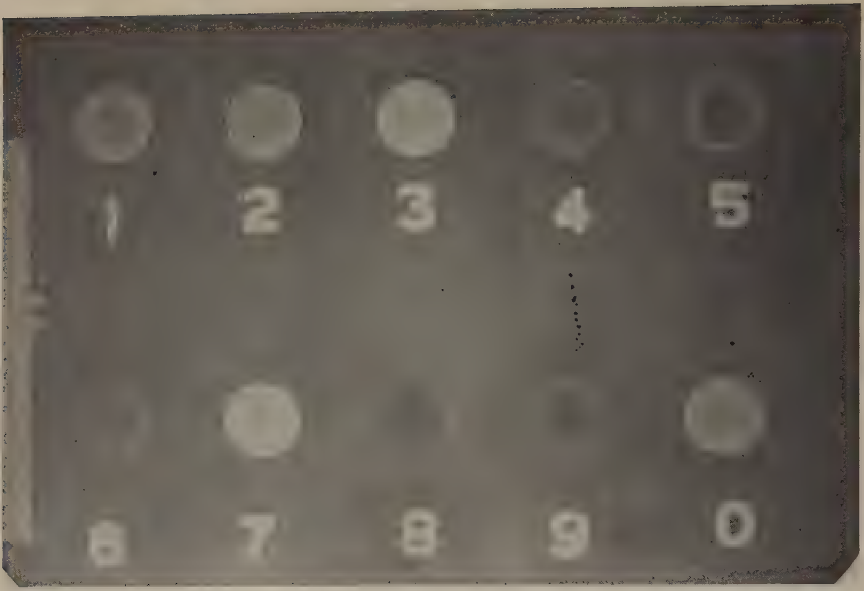

FIGURE 6. Example of experiment of the first type: (1) Pantopaque; (2) Hypaque, 50 per cent; (3) Urokon, 70 per cent; (4) Skiodan, 20 per cent; (5) Diodrast, 35 per cent; (6) zinc EDTA, 8.6 per cent; (7) lead EDTA, 14.5 per cent; (8) cobalt EDTA, 7.5 per cent; (9) barium EDTA, 7 per cent; and (10) cadmium EDTA, 11 per cent.

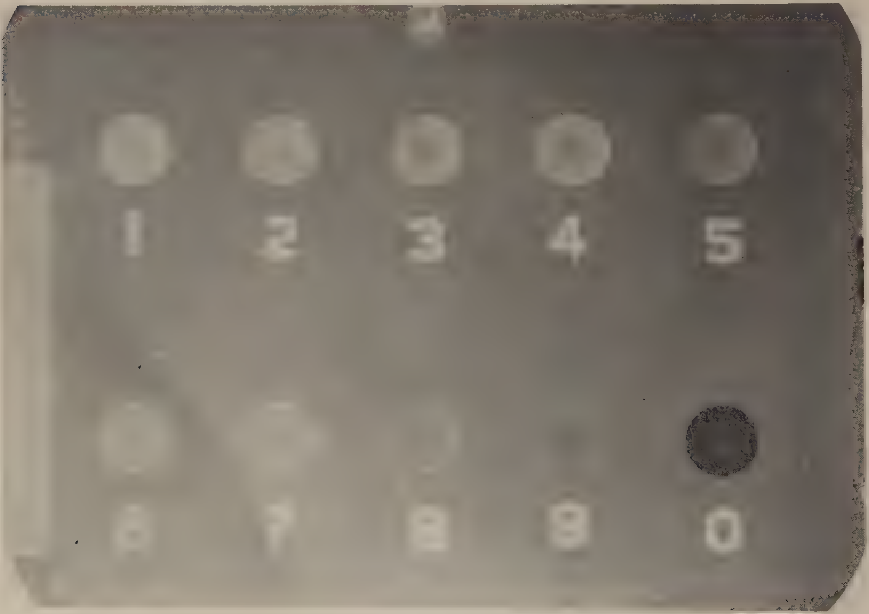

FIGURE 7. Example of experiment of the second type: (1) lead EDTA, 14.5 per cent; (2) lead EDTA, 7 per cent; (3) lead EDTA, 6 per cent; (4) lead EDTA, 5 per cent; (5) lead EDTA, 4 per cent; (6) cadmium EDTA, 11 per cent; (7) cadmium EDTA, 7 per cent; (8) cadmium EDTA, 6 per cent; (9) cadmium EDTA, 5 per cent; and (10) empty.

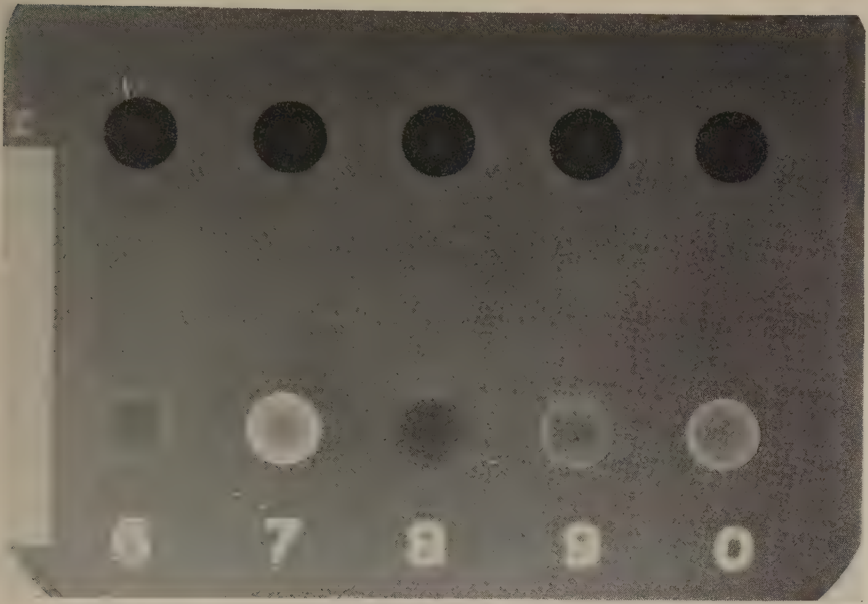

FIGURE 8. Example of experiment of the third type: (6) barium EDTA, 7 per cent; (7) lead EDTA, 7 per cent; (8) cobalt EDTA, 7 per cent; (9) zinc EDTA, 7 per cent; and (10) cadmium EDTA, 7 per cent.

TABLE 4
CONCENTRATIONS* OF CHELATED COMPOUNDS TESTED

1. Lead EDTA, 14.5
2. Lead EDTA, 7
3. Lead EDTA, 6
4. Lead EDTA, 5
5. Lead EDTA, 4
6. Lead cyclohexyl-EDTA, 8
7. Lead DTPA, 8.5
8. Lead DTPA, 8
9. Cadmium EDTA, 11
10. Cadmium EDTA, 8
11. Cadmium EDTA, 7
12. Cadmium EDTA, 6
13. Cadmium EDTA, 5
14. Cadmium 544A, 4
15. Cadmium cyclohexyl-EDTA, 8
16. Zinc EDTA, 8.6
17. Cobalt EDTA, 7.5
18. Copper EDTA, 4
19. Nickel EDTA, 2.4
20. Barium EDTA, 8.6
21. Barium EDTA, 7.3
22. Barium EDTA, 7
23. Barium EDTA, 6
24. Barium EDTA, 5
25. Bismuth EDTA, 7.5
26. Bismuth EDTA, 6
27. Bismuth EDTA, 5
28. Cerium EDTA, 5.8
29. Cerium EDTA, 5
30. Cerium EDTA, 4
31. Cerium EDTA, 3.5

* In percentages.

expected,[12, 13] that a strict relationship exists between X-ray opacity and the atomic number of the metal in the compound. The higher the atomic number, the higher the opacity. Also, as is obvious, the opacity of the solution was found to be higher in relation to the concentration of the metal. The higher the concentration, the higher the opacity. X-ray opacity comparable to the

TABLE 5

COMPOUNDS TESTED *IN VIVO*

Abbreviation	Compound
EDTA	Ethylenediaminetetraacetic acid
Cyclohexyl-EDTA	1,2-Diaminocyclohexane(N,N′-tetraacetic acid)
DTPA	Diethylenetriamine pentaacetate
544^A	N,N′-(2-hydroxycyclohexyl)ethylenediaminediacetic acid

TABLE 6

ADMINISTRATION OF TEST SUBSTANCES

Compound and concentration (%)	Form or site of administration
Lead EDTA, 8	Intravenous (IVP)
Lead DTPA, 8.5	Intravenous (IVP)
Lead cyclohexyl-EDTA, 8	Intravenous (IVP)
Cadmium EDTA 8,	Intravenous (IVP)
Cadmium cyclohexyl-EDTA, 8	Intravenous (IVP)
Barium EDTA, 7.3	Gastrointestinal study
Cadmium 544^A, 4	Gastrointestinal study
Lead DTPA, 8	Intravenous (phlebography)
Cerium EDTA, 5.8	Intracardiac (cardiography)
Lead DTPA, 8	Cisterna magna (myelography)

opacity of the above-mentioned iodinated contrast media was considered "good." In some cases the opacity of the material under observation was less than that of moderately concentrated iodinated compounds commonly used as radiographic contrast material; this opacity, however, was still considered "useful," and the compound was studied *in vivo*.

When the experiments *in vitro* had shown that the opacity of a solution was good or, in some instances, useful, experiments *in vivo* were carried out. TABLE 6 lists the compounds used in the *in vivo* experiments. Dogs and rabbits were used as the experimental animals, and the compounds were given intravenously, orally, intracardiacally, and injected into the cisterna magna. Urographies, phlebographies, G.I. studies, cardiographies, and myelographies were so obtained. The quantity of material injected was varied for the different compounds used, chiefly according to the concentration of the metal in the solution, its X-ray opacity previously proved *in vitro*, and the weight of the animal. Accurate toxicological studies were carried out for only some of the substances under study. The technical quality of the films obtained varied in the different types of examination. Satisfactory diagnostic studies were obtained in several instances (FIGURES 9, 10, and 11).

It is important to stress the fact that the toxicity of the compounds we have tried is high—definitely higher than that of the standard iodinated compounds in concentrations such that they may give a corresponding degree of opacity. Most of the substances injected were not well tolerated by the animals. Much,

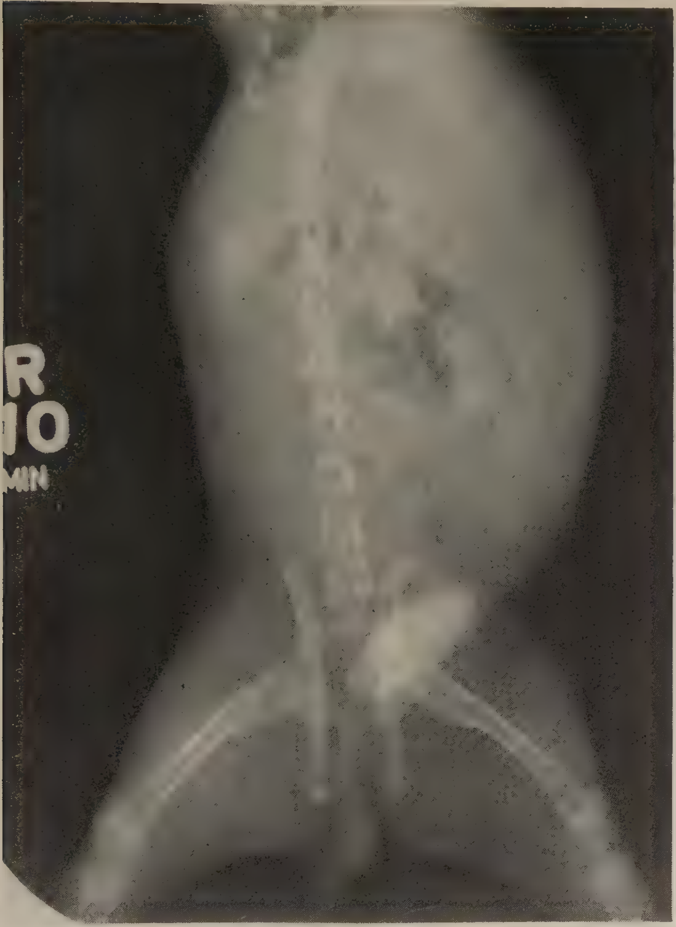

FIGURE 9. Intravenous pyelography in rabbit.

therefore, must yet be done to establish the relative toxicity of the different chelated compounds before attempting their clinical use.

Selective Organ Localization of Metal Chelates

Contrast media now available offer the possibility of selective visualization of various organs and body structures through the ability of the media to concentrate in selected areas of the body. These results have been attained by persistent and ingenious manipulation of the organic molecules that serve as the carriers of the contrast element. Do the same possibilities exist for chelates?

In a preliminary investigation we have utilized tracer radioactive iron as a readily detectable metal for following the excretion pattern of a series of iron

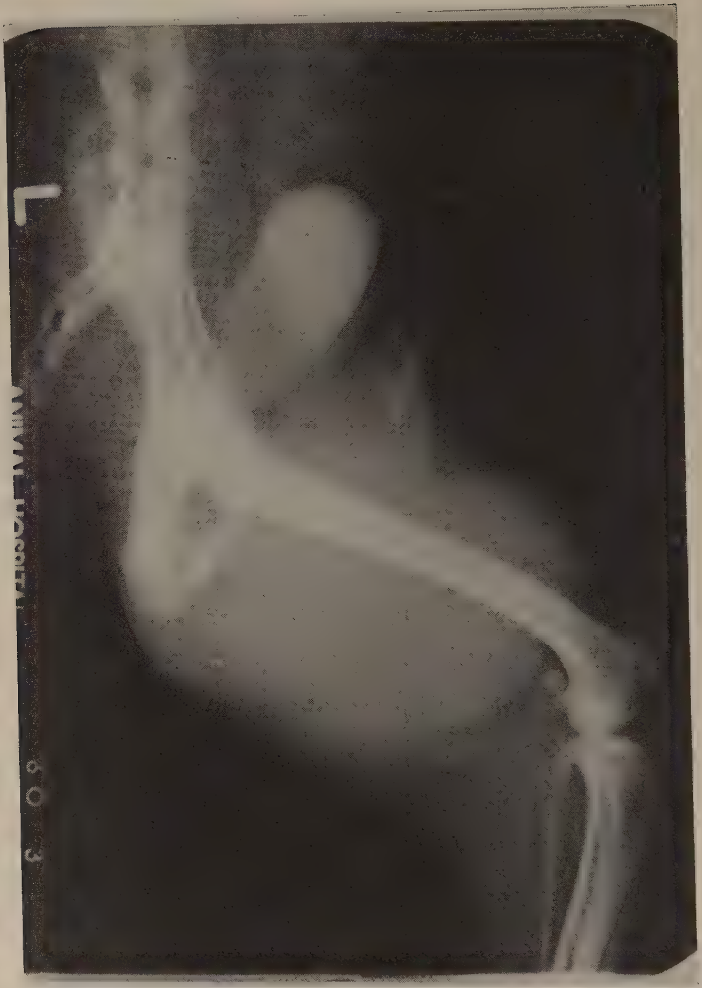

FIGURE 10. Intravenous pyelography in dog (systogram).

chelates of varied structure. TABLE 7 lists a number of the chelate compounds studied in this survey and the urinary and fecal iron excretion in rats, following intraperitoneal administration of the chelates.

Several points in this aspect of the study are of interest in connection with the general problem of the possible utilization of chelates as contrast agents. First, one may note for the selected group of iron carriers that it is possible to induce nearly quantitative excretion of iron by proper choice of carrier. This is of striking significance when one considers that the body has no available physiological mechanism for the excretion of large quantities of iron. Second, by modification of the chemical nature of the carrier, the route of the excretion

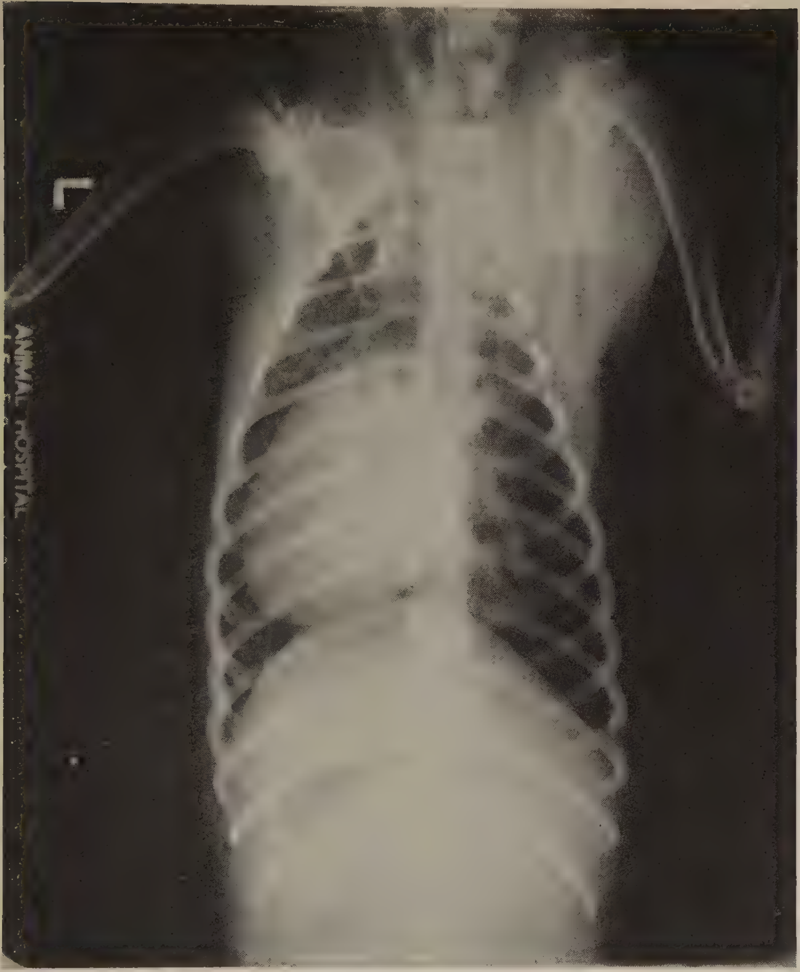

FIGURE 11. Myelography in dog.

following parenteral administration may be varied from one that is almost entirely genitourinary to one that shows a significant gastrointestinal component. It is our belief that this alteration of the direction of excretion of this chelated metal is a reflection of the change in the solubility characteristics of the compound. The iron chelate of 1,2-diaminocyclohexanetetraacetic acid is highly hydrophilic. In contrast, the increasing bulk of the cycloaliphatic rings and the decrease in the number of charged groups in the iron chelates of the last 2 compounds of TABLE 7 confers some lipotropic character on the compounds. This change is reflected in the altered distribution pattern of this sequence of compounds. The hydrophilic compounds are excreted by the re-

TABLE 7
EXCRETION OF RADIOACTIVE CHELATED IRON
I.P. Administration in Rat

Compound	Percentages excreted		
	Urine	Feces	Total
1,2-Diaminocyclohexane(N,N′-tetraacetic acid)	90.1	6.4	96.5
Ethylenediaminetetraacetic acid	55.8	14.3	70.1
Beta-hydroxyethylethylenediaminetriacetic acid	54.8	4.5	59.3
2-Hydroxycyclohexylethylenediaminetriacetic acid	60.5	18.5	79.0
N,N′-(2-hydroxycyclohexyl)ethylenediaminediacetic acid	52.8	28.1	80.9

nal route after parenteral administration, while the shift to some lipotropic character has served to bring about a significant shift to the biliary and fecal pathways for the less polar materials.

In summary, we believe that metal chelate compounds offer a possible means of utilization of the pronounced opacity of the metals for the purposes of X-ray contrast media. The problems that must be solved before materials of this class can be safely used for clinical study are formidable. It is clear, however, that these difficulties are not insurmountable and that the intensive study required may be justified by the significant advances in diagnostic radiology that inevitably follow the introduction of new materials and methods.

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A NEW CATEGORY OF CONTRAST MEDIA: WATER-SOLUBLE RADIOPAQUE POLYVALENT CHELATES*

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The search for ideal contrast media for radiodiagnostic studies has extended over many decades. Although many serviceable contrast media have been developed and are now in clinical use, all the properties of an ideal contrast medium have never been captured in a single preparation. It is well known that each of the available contrast media has particular, though not necessarily prohibitive, disadvantages.

This paper will describe briefly the application of polyvalent-metal chelates as contrast media in bronchography and angiocardiography in anesthetized dogs. Because certain chemical and physical properties are possessed by heavy-metal chelates, this group of compounds may be studied profitably for potential use as contrast media. Literally, scores of compounds in this category remain to be synthesized and investigated.

Sapeika,[1-3] in 1954, was the first investigator to report the use of polyvalent-metal chelates as contrast media. He used Pb-ethylenediaminetetraacetate (PbEDTA) in a variety of experimental animals and, later, in human beings.[4] Following this lead, in 1956, Migliorini and Toddei[5] in Italy and Shapiro[6] in this country published their observations on the use of PbEDTA as a contrast medium in animals. These authors all have been hopefully impressed with this use of this chelate.

Chelation has been defined as a reversible reaction between a polyvalent metallic ion and a polyaminocarboxylic acid to form, within the molecule, one or more heterocyclic ring structures, incorporating the metallic ion by both electrovalent and covalent bonds. The metallic ion thus becomes firmly bound and unavailable for chemical or physiological activity. The reaction product is called a chelate, a name derived from the Greek *chele*, meaning claw, which is descriptive of the "clawlike" structure of the chelate. The physical and chemical properties possessed by some heavy-metal chelates include (1) excellent radiopacity, (2) crystalline structure, (3) solubility in water, (4) physiological inertness within dosage limits, and (5) rapidity of excretion through the genitourinary tract and, to a lesser degree, the gastrointestinal tract.

The literature dealing with the theoretical aspects of chelation chemistry is enormous. However, a brief statement of some pertinent basic concepts will be helpful. The reversible reaction of a chelate and the polyvalent metal is depicted:

$$\mathrm{Me}^{++} + (\text{Chelate Acid}^{=}) \rightleftharpoons (\text{Me Chelate})$$

The equilibrium constant, K_e, is a measure of the extent to which chelation

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* The study reported in this article was supported by the Research Corporation of the Detroit Receiving Hospital.

TABLE 1

RESULTS IN BRONCHOGRAPHY WITH BiDTPA

Dog	Weight, kg.	Amount of Bi medium stock solution* instilled, ml.	Saline dilutions of Bi medium (saline)	Total administered dose of medium as grams of Bi/kilogram	Fate
1	12.3	1.5	3:1	0.029	Lived
2	12.7	2.25	3:1	0.042	Died as anesthetized I.V.
3	12.3	3.0	3:1	0.057	Lived
4	10.9	4.5	3:1	0.097	Lived
5	15.0	2.0	none	0.031	Lived
6	15.4	3.0	none	0.046	Lived
7	17.7	4.0	none	0.053	Lived
8	13.1	6.0	none	0.108	Lived
9	10.9	3.5	7:1	0.076	Lived
10	13.2	5.25	7:1	0.094	Lived

* Stock solution: disodium bismuth diethylenetriamine pentaacetate—*p*H, 7.58; molarity, 1.12; bismuth content, 0.2326 gm./ml.

formation occurs:

$$K_e = \frac{(\text{Me Chelate})}{(\text{Me}^{++})(\text{Chelate Acid}^{=})}$$

From this ratio it can be seen that where K_e is large, the ion concentration of the free metal will tend to be low. The value of K_e may be affected by several factors. Increasing the *p*H in general tends to increase the value of K_e. Increases in temperature tend to reduce the value of K_e, although to only a slight degree. Use of the Na salts of the chelate acid results in increased solubility, in increased values for K_e and, depending upon the number of Na ions per chelate molecule, in a related increase in *p*H. Consequently, the chelates considered for use as contrast media should have the highest possible K_e value at or near blood *p*H and should contain enough Na ions per molecule to assure maximum water solubility without increasing the *p*H beyond physiological limits.

Methods

Mongrel dogs anesthetized with intravenously administered 6 per cent sodium Nembutal were used throughout all series. In the bronchography studies, after each dog was anesthetized,* the right pulmonary bronchus was intubated, the radiopaque chelate, disodium bismuth diethylenetriamine pentaacetate (BiDTPA),† instilled, and the rubber catheter withdrawn. Chest X rays of each animal were taken, spaced at 4 irregular intervals: (1) immediately after instillation of the chelate, (2) between 31 and 55 min. after instillation, (3) 24 hours after instillation, and (4) 1 month after instillation. The dogs were anesthetized prior to each of the X-ray studies. Ten dogs were used in the bronchography series (TABLE 1).

* Toleration in conscious subjects is not known.

† BiDTPA and other chelates mentioned in this paper were synthesized by the Geigy Chemical Corporation, Ardsley, N. Y.

In the angiocardiographic studies the dogs were anesthetized, the external jugular vein injected percutaneously, and the X rays taken simultaneously with the injection of the medium. In this study there were 2 series. The first series used 11 dogs injected intravenously with BiDTPA (TABLE 2); the second series deals with another group of 6 dogs injected with BiDTPA and the calcium analogue (TABLE 3). Dog 3 (TABLE 2), on a dosage of bismuth chelate

TABLE 2

RESULTS WITH INTRAVENOUS USE OF BiDTPA STOCK SOLUTION IN ANGIOCARDIOGRAPHIC STUDIES

Dog	Weight, kg.	Bi medium stock solution* administered I. V., ml.	Total administered dose of Bi medium as grams of Bi/kilogram	Fate
		First Group		
1	15.4	10.0	0.16	Lived
2	14.5	10.0	0.16	Lived
3†	11.8	10.0	0.20	Lived
4	20.2	6.0	0.07	Lived
5	11.6	12.5	0.25	Died‡
		Second Group		
6	10.9	7.8	0.21	Lived
7	14.5	11.0	0.22	Lived, hindquarter paralyzed
8	10.4	8.0	0.23	Died, hindquarter paralyzed
9	11.8	9.8	0.24	Lived
10	11.3	9.7	0.25	Lived
11	16.8	15.0	0.26	Lived

* Stock solution for first group: bismuth diethylenetriamine pentaacetate—*p*H, 7.58; molarity, 1.12; bismuth content, 0.2326 gm./ml. Stock solution for second group: bismuth diethylenetriamine pentaacetate—*p*H, 7.43; molarity, 1.40; bismuth content, 0.2911 gm./ml.

† Angiocardiogram shown in FIGURE 4.

‡ Typical microscopic lesions produced are shown in FIGURE 6.

TABLE 3

EXPERIENCE WITH THE SIMULTANEOUS USE OF BiDTPA AND THE CALCIUM ANALOGUE

Dog	Weight, kg.	Bi medium stock solution* administered I. V., ml.	Ca analogue stock solution† administered I. V. with Bi medium, ml.	Total administered dose of Bi medium as grams of Bi/kilogram	Fate
1	11.4	15	5	0.31	Lived
2	13.6	15	5	0.29	Died
3	11.4	15	5	0.31	Lived
4	9.6	15	5	0.42	Died
5	8.2	15	5	0.49	Died
6	8.2	15	5	0.49	Died

* Stock solution: disodium bismuth diethylenetriamine pentaacetate—*p*H, 7.58; molarity, 1.27; Bi content, 0.2659 gm./ml.

† Stock solution: disodium calcium diethylenetriamine pentaacetate—*p*H, 7.22; molarity, 1.46; Ca content, 0.0589 gm./ml.

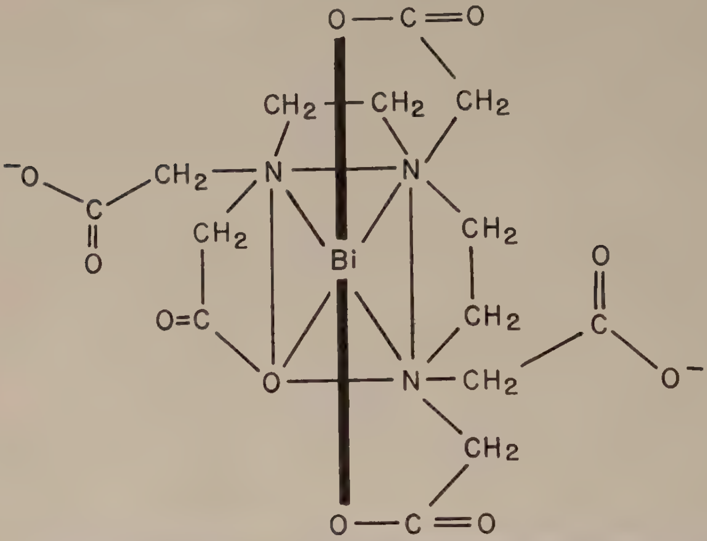

FIGURE 1. Structural formula of bismuth diethylenetriamine pentaacetate. Two ions of Na may be associated with this compound. Heavy bars represent electrovalent bonds on the bismuth; smaller bars represent covalent bonds.

containing 0.25 gm./kg.,* died within 3 days. Dogs 6 to 11 were tested with varying doses of intravenously administered Bi chelate in an attempt to establish the MLD; the LD_{50} remains to be established. Two dogs developed a bilateral paralysis of the lower extremities, a phenomenon not previously observed in any of the dogs treated with BiDTPA.

Results in Bronchography

The radiopaque chelate used for bronchography was BiDTPA (FIGURE 1). This compound has a high order of stability *in vitro*.† The experimental data on the 10 dogs in this series are summarized in TABLE 1. These studies constitute the first recorded application of radiopaque chelates as contrast media in bronchography.

Bronchograms of perfectly acceptable diagnostic quality (FIGURE 2*a*) were obtained on all 10 dogs within the dosage range cited. The dilution of BiDTPA with saline (TABLE 1) was found to be unnecessary. The most satisfactory bronchograms were obtained with full-strength stock solutions. Rapid mobilization of the water-soluble BiDTPA from the bronchi was evidenced in most cases by a marked blurring or fading of the contrast medium as demonstrated in the bronchograms taken 31 to 55 min. after the original instillation (FIGURE 2*b*). No contrast medium can be detected in films taken 24 hours (FIGURE 2*c*) and 1 month (FIGURE 2*d*) after instillation.

There was 1 death in this series. Dog 2 suddenly expired as the anesthetic agent was being administered intravenously in preparation for the third X-ray study 24 hours after instillation of the media. At autopsy on this dog there was demonstrated a severe confluent bilateral bronchopneumonia. Microscopically the kidneys were hyperemic, and there was acute passive congestion in the liver. The dose of the contrast medium given this dog was relatively small; six larger doses (to twice as much) were administered in surviving dogs (TABLE 1). For these reasons we believe it probable that the death of this dog was due to causes other than the toxicity of the bismuth chelate.

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* All doses of the chelates are stated in terms of the bismuth content expressed as grams of bismuth per kilogram.

† According to M. Dexter, Geigy Pharmaceutical Co., Yonkers, N. Y., the amount of metal released from bondage with the chelating agent is exceedingly small—about 10^{-12} M.

It is of interest to compute the theoretical dosage of BiDTPA required for bronchography in an adult human being and to compare this to the range of dosage administered in surviving dogs. If 10 ml. of the stock solution of BiDTPA used (bismuth content 0.2326 mg./ml.) were administered to a 70-kg. patient, the dose of chelate expressed in terms of bismuth would be 0.032 gm./kg. Comparison with the data in TABLE 1 shows that dogs receiving 3 times this dosage survived without morbidity.

In earlier similar experiments on dogs originally used for bronchography and subsequently subjected to angiocardiography there was found at autopsy in 1 animal a pulmonary nodule approximately 0.3 cm. in greatest dimension, consisting microscopically of discrete, multiple masses of pale-blue homogenous material that was associated with giant-cell formation (FIGURE 3). These masses varied from 20 to 200 μ in diameter. Whether they represent BiDTPA is not clear. If such nodularity developed subsequent to the instillation of BiDTPA, one would have expected to find a nodular or miliary radiopaque pattern on X rays taken during the 30-day period; such was not the case.

Similar homogenous material was observed in the lumen of a major bronchus without inflammatory cellular reactions or alteration of the bronchial epithelium. Since nodular aggregates of Bi chelate would retain their radiopacity, if such lesions were of significant frequency their presence in other dogs in the series would probably exhibit a nodular or even miliary radiopaque pattern in the X-ray studies. This was not observed.

The observations on the use of BiDTPA for bronchography may be summarized as follows:

(1) Bronchograms of diagnostic quality were obtained.

(2) There is rapid absorption and mobilization of the water-soluble contrast medium from the lungs.

(3) There appears to be no acute or delayed morbidity within dosage limits. In one autopsied animal a nonsuppurative, low-grade inflammatory nodule was noted that may be related to the use of the Bi chelate.

(4) Orders of dosage of the chelate three times the dose theoretically required for diagnostic bronchograms in human beings were well tolerated by mongrel dogs.

(5) This successful application of radiopaque chelates as contrast media in bronchography may be prophetic of ultimate clinical utility.

Results in Angiocardiography

For angiocardiography the results to date are not as definitive as for bronchography. Unexpected problems of chelation stability in plasma were en-

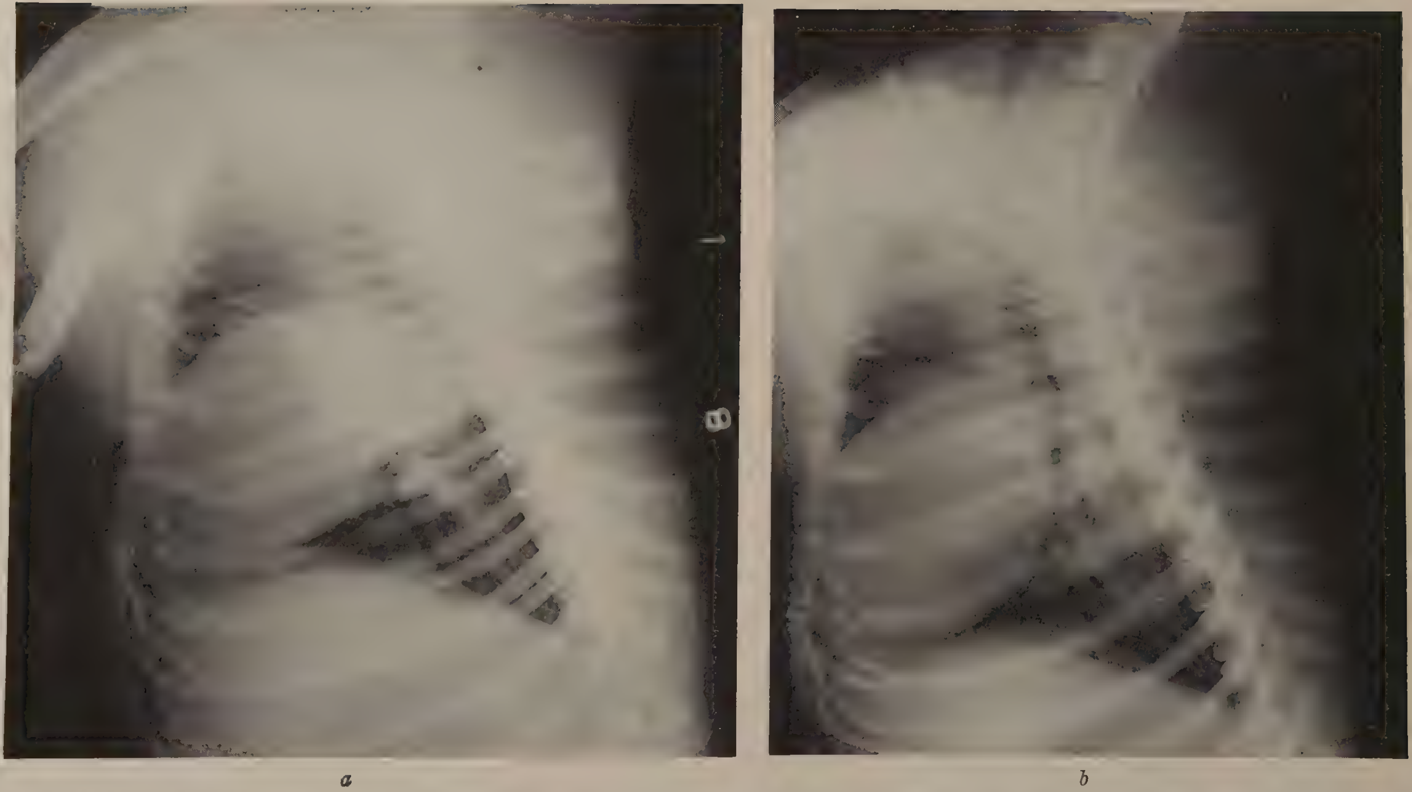

FIGURE 2. (*a*) Bronchogram of Dog 8 (TABLE 1), taken immediately after BiDTPA had been instilled in the right main stem bronchus, is of diagnostic quality; note the alveolar detail. Radiopacity of the medium, even against the heart shadow, compares favorably with that of bone. (*b*) Chest X ray of the same dog, taken 38 min. after first X ray, clearly demonstrates mobilization of the medium from the bronchial passages and the alveoli. Absorption of the medium has progressed beyond the point of "blurring."

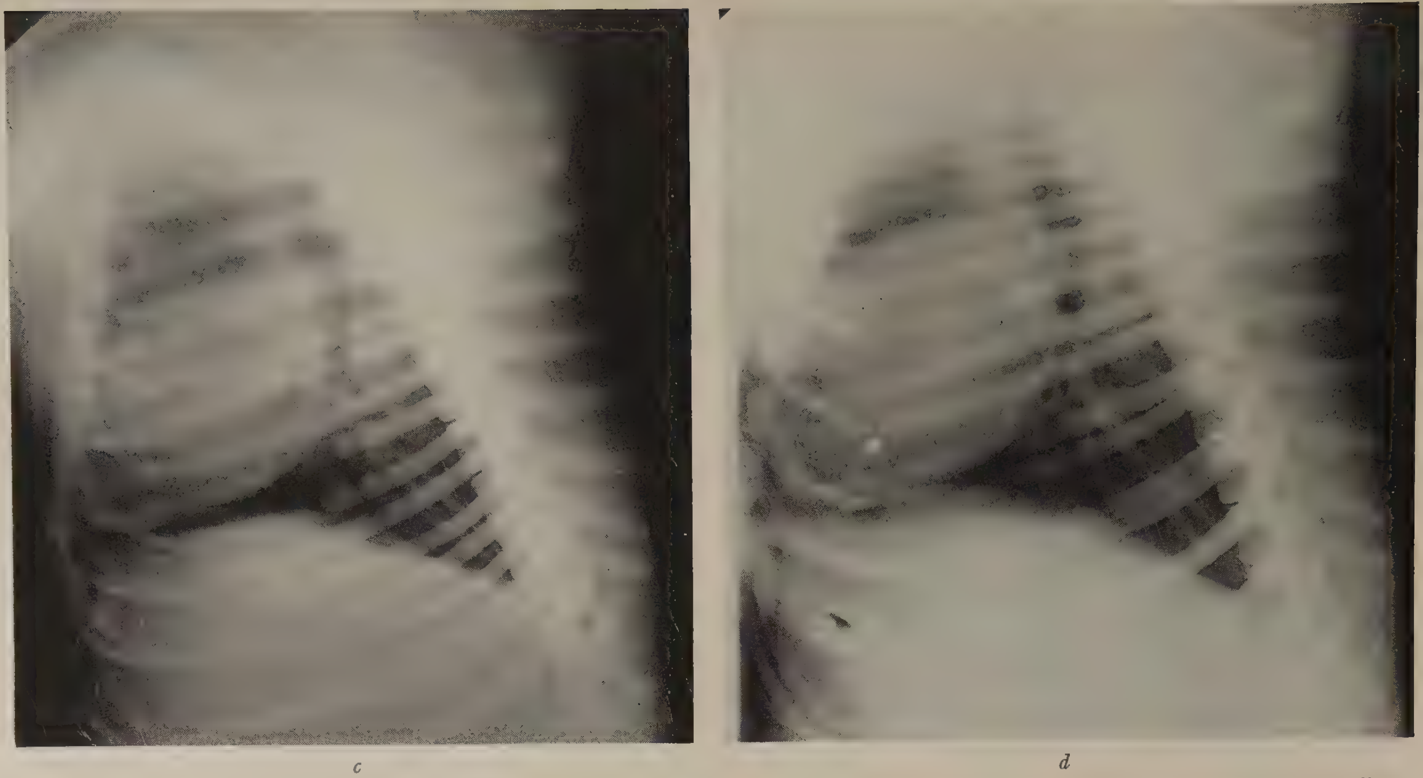

FIGURE 2. (*c*) Chest X ray of the dog of FIGURE 2*a* and *b*, taken 24 hours after first X ray. There is no evidence of radiopaque medium within the lung parenchyma; bronchovascular markings are present. (*d*) Chest X ray of the same dog, taken 30 days after first X ray, represents normal canine chest. There is no evidence of nodular aggregates of radiopaque medium. The dense granular shadow overlying the heart is an artifact caused by a soiled casette, and is reproduced on other X rays taken with it.

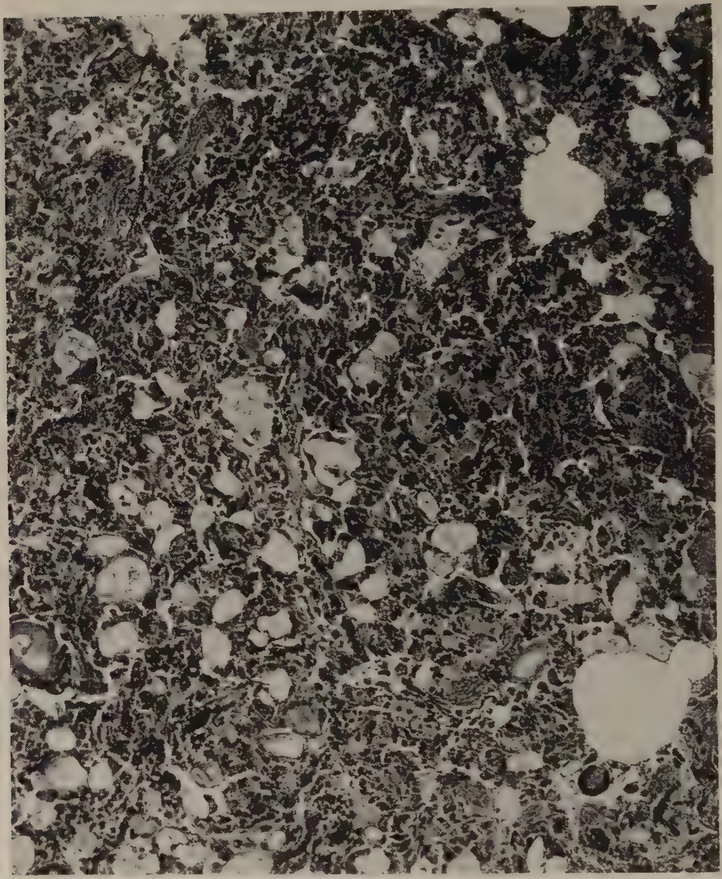

FIGURE 3. Section of the pulmonary nodule described in the text. (Hematoxylin and eosin, ×160.)

countered, and the experimental work directed to its solution has not yet confirmed entirely a theoretical solution that is discussed below.

In these studies, the intravenous administration of the BiDTPA results in technically excellent angiocardiographic studies (FIGURE 4). It will be noted that the radiopaque density of the medium in FIGURE 4 compares favorably with that of bone. Dosages of BiDTPA reduced 20 per cent produced diagnostically useful studies. Fifty-five minutes after an angiocardiographic study in a preliminary series (not reported in this article) an X ray of the abdomen was taken; it will be noted that in this X ray (FIGURE 5) the urinary bladder is distended and contains radiopaque medium. This is indicative of the rapid clearance of the chelates from the plasma by the kidney. In human subjects given 18 ml. of a 50 per cent solution of PbEDTA intravenously, Sapeika[4] demonstrated that pyelograms could be obtained at 1-min. intervals for 3 to 27 min. after injection.

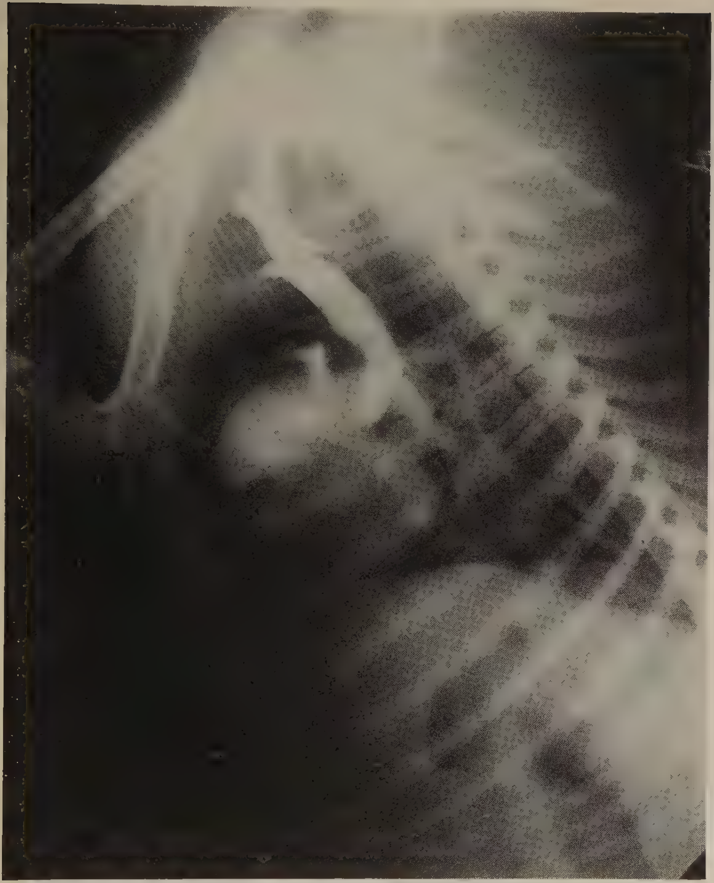

FIGURE 4. Angiocardiogram obtained by injecting BiDPTA directly into the external jugular vein of a surviving dog (No. 3, TABLE 2). The radiopaque quality of the medium compares favorably with that of bone. Demonstrated are the external jugular vein, the superior vena cava, and the right auricle.

In the intravenous use of bismuth chelates, as might be expected, the dose of the chelate is of critical importance. The useful dose and the minimal lethal dose (MLD) are disconcertingly approximate. TABLE 2 summarizes our experience in the use of intravenously administered BiDTPA in angiocardiographic studies in a series using 11 dogs. Dogs 5 and 8, receiving doses of the chelate of 0.23 gm./kg. and 0.25 gm./kg., respectively, died. However, dogs 9, 10, and 11, receiving doses in somewhat the same range, survived. Thus the useful dose (0.20 gm./kg., dog 3, TABLE 2) is within 0.03 gm./kg. of the MLD. In dogs 1 and 2 (TABLE 2) receiving doses of 0.16 gm./kg. of the chelate, very adequate angiocardiograms were obtained; thus the MLD and useful dose could differ by as much as 0.07 gm./kg. This is still not within acceptable limits.

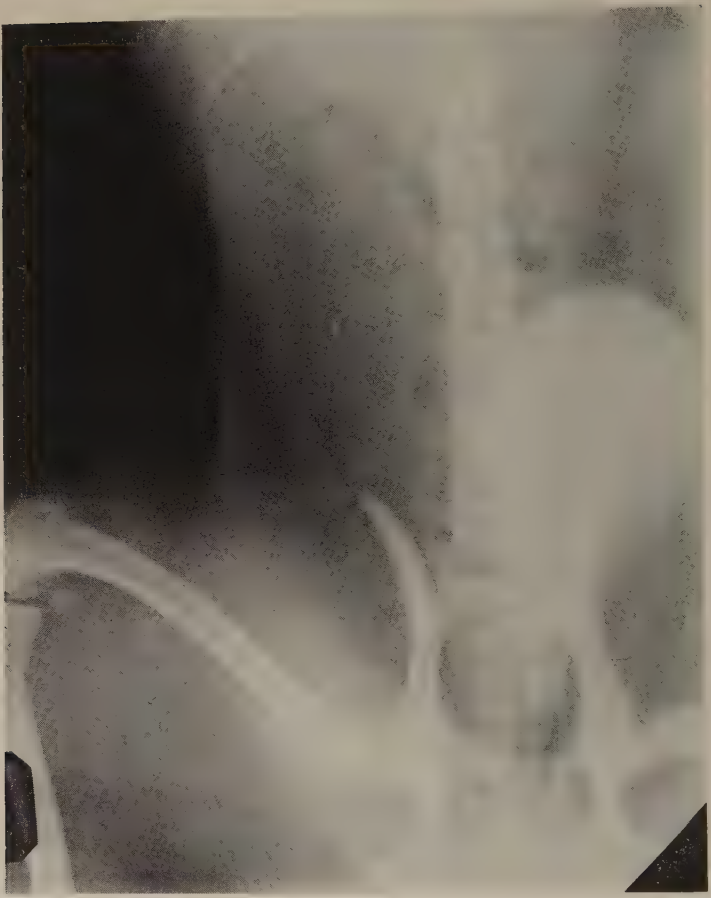

FIGURE 5. Flat plate of the canine abdomen taken 55 min. after angiocardiography.

Autopsy studies on expired dogs in this series demonstrated lesions in the kidneys only. These consisted of mineral deposition in the thickened Bowman's capsules (FIGURE 6). There was similar mineral deposition in the walls of some of the blood vessels and within the lumen of some tubules. Evidence of acute tubular epithelial degeneration and necrosis was present. The glomeruli appeared normal, and sections of other tissues were not remarkable; the central nervous system was not examined.

Since the lesions in the kidneys were consistent with "bismuth nephritis," it was considered probable that the bismuth ion escaped in significant quantities from the chelate bond. The reason for such a change in the chelation stability in the plasma is a matter for conjecture. Nevertheless, it appeared reasonable that this problem could probably be eliminated by increasing the stability of the bismuth chelate within the blood stream. This was attempted by applying two well-established chemical principles:

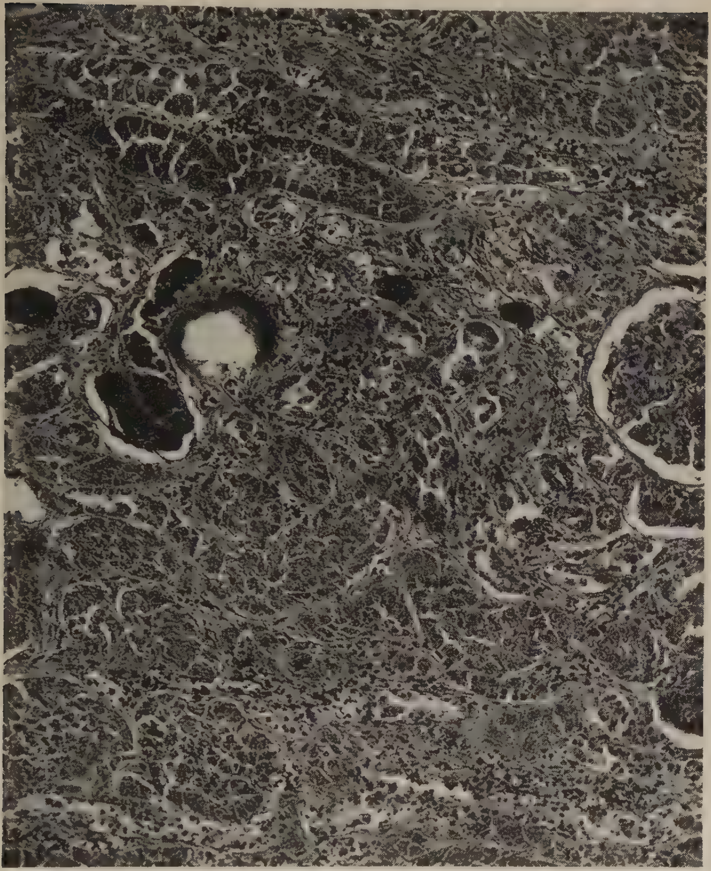

FIGURE 6. Section of a kidney from a dog administered a lethal intravenous dose of BiDPTA (stock solution). The dark granular material represents mineralized necrotic debris of a tubule, with preservation of the basement membrane. The prominent semilunar figure of similar material partially encircling a clear space represents mineralization of Bowman's capsule. The histological picture is entirely compatible with the effect of heavy metals on the kidney. (Hematoxylin and eosin, ×90.)

(1) *The Le Chatelier principle.* This involves the use of the "common ion" effect. By increasing the concentration of the chelate acid in the plasma, the reaction is forced to the right or chelate form.

(2) *Displacement reactions.* It should be stated that in chelation systems there is an order of displacement for competing metallic ions such that the heavier metallic ions will usually displace the lighter in the chelate molecule. Accordingly, there can be supplied in the plasma (together with the Bi chelate) a secondary chelating system competing for ionic bismuth. It can be appreciated then that by the use of the above two principles the concentration of ionic bismuth in plasma would be forced to an irreducible minimum and, at the same time, the concentration of chelated bismuth in plasma would be at a maximum.

The calcium analogue of the chelate was chosen to enhance the chelation of bismuth since this one compound served both the above principles. An additional consideration in the selection of the calcium analogue was that chelation of plasma calcium (and its attendant hazards) would be avoided. Therefore, CaDTPA was prepared with the intent of mixing quantities of it with BiDTPA just prior to injection of the mixture.

Accordingly, in a series of 6 dogs, intravenous doses of BiDTPA of a lethal order were administered (TABLE 3) together with a quantity of CaDTPA. These were mixed in the syringe just prior to injection. From TABLE 3 it will be seen that, since 15 ml. of 1.27 M BiDTPA (19.1 mmoles) was mixed with 5 ml. of 1.46 M CaDTPA (8.3 mmoles), there was administered in each injection in the series a millimolar excess of BiDTPA over bismuth of about 43.5 per cent. Thus simultaneous introduction of the calcium analogue and the bismuth chelate into the blood stream produced an excess of "common ions" and a secondary chelation system competing for bismuth ions. If the ancillary use of the calcium analogue were effective, it would follow that the tolerance for BiDTPA and, therefore, the MLD should increase. Where previously (TABLE 2) a dose of 0.23 gm./kg. was lethal, in this series (TABLE 3), with the simultaneous use of the bismuth chelate and the calcium analogue, the MLD shifts equivocally somewhat higher. Consequently, while concomitant use of the bismuth chelate and the calcium analogue to enhance chelation of the bismuth has an intriguing theoretical basis chemically, our experimental efforts to prove it must be considered at best only suggestive.

We believe our failure in this regard is due to the following:

(1) The MLD was determined instead of the LD_{50}; determinations of the LD_{50} with a larger statistical base are required.

(2) Optimal proportions of the mixture of the bismuth chelate and the corresponding calcium analogue were not determined by us;* our preliminary results are based on proportions that were casually selected.

Therefore, we believe that when the LD_{50} of the intravenous dose of the chelates is determined, and when the optimal proportions of a mixture of the chelate and the calcium analogue are determined, such a mixture will probably increase the tolerance of the subject for intravenously administered chelates. This will be demonstrated by a higher LD_{50} with the calcium analogue than will be possible without it.

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* In a series of angiographic studies in 5 dogs (not reported in this article) and using, as the radiopaque chelate, sodium bismuth diaminodiethylether tetraacetate with the calcium analogue in multiples of the lethal dose, it was found that the small doses of the analogue did not protect the dogs against death. The mortality rate in the series was 100 per cent. Upon injection, several of the dogs developed rigidity immediately, lost sphincter control, and expired. An identical experience was had with the use of disodium lead cyclohexane tetraacetate and its calcium analogue in comparable dosage levels in another series of dogs (also not reported in this article).

The experience in these last two series does not gainsay the value of the protective effect of the simultaneous use of the bismuth chelate and calcium analogue. The toxic doses in these series were multiples of the minimum lethal dose. The quantities of calcium analogue used were only fractional molar equivalents. Thus, assuming that the calcium analogue "buffered" bismuth to its capacity, enough moles within the toxic range of Bi chelate to cause death were still present.

These series are to be considered an attempt at determining optimal proportions of the bismuth chelate and the calcium analogue, a problem that still requires solution.

Discussion

This paper has been entitled in part "A New Category of Contrast Media" to emphasize that, although we have discussed in detail only one chelate, BiDTPA, there are literally scores of chelates available and theoretically possible. It has been our purpose to demonstrate the chemical and physical properties of this category of compounds in terms of a prototype, BiDTPA.

The properties of particular interest include aqueous solubility and rapid mobilization from the bronchial tree, as demonstrated by the sequential bronchograms. The cystogram taken within 1 hour after angiocardiography demonstrates the rapid removal of the chelate from the plasma by the kidney. Although excretion studies are not as yet available for many of the chelates that may be considered for use as contrast media, the literature does contain numerous studies on the excretion of ethylenediamine tetraacetate (EDTA), 1 of the more simply constructed chelating agents. Studies[7, 8] have demonstrated that EDTA was eliminated from 93 to 98 per cent in 24 hours in human beings. The demonstrated technical excellence of the X ray studies is a measure of the degree of radiopacity that may be achieved with this category of compounds.

Within the scope of the angiocardiographic series of experiments and with the limited numbers of subjects in each of those series, no firm statements can be made as to the prophylactic or protective effect of adding the calcium analogue to the chelate to assure maximum chelation stability of the compound in plasma. Nevertheless, the results here seem to suggest that the concept is worthy of further investigation. Sapeika has suggested a related approach to this problem.[1, 4]

We believe that enough preliminary evidence exists to warrant the vigorous investigation of the suggestion that an ideal water-soluble contrast medium may well be developed from among the scores of radiopaque polyvalent chelates still to be synthesized, investigated, or both.

Summary

The use of water-soluble polyvalent chelates as contrast media is suggested on the basis of their physical and chemical properties. Applications of this concept are cited from the very brief total literature on this subject.

Chelation is defined and the pertinent chemical principles of chemistry involved are briefly reviewed.

Dosage and mortality data and bronchographic and angiocardiographic roentgenograms in dogs are presented. The rapid mobilization of the chelate from the lungs and blood stream is evident in this material.

For the first time radiopaque chelates have been used successfully as contrast media in bronchography. The encouraging results may be prophetic of ultimate clinical application.

Pulmonary and renal lesions associated with the use of chelates are demonstrated.

An attempt to increase the stability of the bismuth chelate within the plasma by the simultaneous use of the calcium analogue of the compound is discussed;

this is considered feasible and worthy of further investigation. Optimal proportions of a mixture of a chelate and its calcium analogue remain to be determined.

The data presented herein are considered merely indicative of the promising potential of radiopaque chelates as contrast media. The active investigation of the scores of available radiopaque chelates for use as contrast media may well result in the discovery of an ideal water-soluble contrast medium.

Acknowledgments

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UNIFORM COLLOIDAL DISPERSIONS FOR HEPATOLIENOGRAPHY*

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Introduction

Particulate colloids injected into the blood stream are removed from circulation by the reticuloendothelial system and deposited principally in the liver and spleen. Thus a natural route exists for the opacification of the liver and spleen by the injection of insoluble, colloidally dispersed contrast agents. Colloidal thorium dioxide (Thorotrast†) gives excellent opacification, but pathological changes in the tissues of localization have resulted from the permanently fixed material and from the radioactivity of thorium.[1] The goal of the research described in this article is a colloidal contrast agent capable of temporary fixation and followed by gradual metabolic breakdown.

The phagocytosis of a colloidal contrast agent consists of an interaction of the organism with both the physical state and the chemical composition of the injected material. The optimum physical requirements for a contrast agent can be defined by the use of biochemical inert particles of measured physical properties in a variety of particle-size ranges. The investigation of organic iodine compounds of low solubility but slight metabolic reactivity should lead to the selection of a radiopaque compound with the desired chemical properties. The information derived from experiments with the inert material should define the physical form in which a chemically satisfactory iodine compound must be prepared. The inert compound chosen for the study of physical properties was polystyrene in the form of a monodisperse latex of spherical particles. The search for a compound chemically suitable as a potential colloidal contrast agent was begun among the derivatives of tetraiodophthalic anhydride.

Polystyrene Dispersions

Polystyrene particles are incapable of chemical reaction with the soluble components of the blood stream and are not likely to aggregate after injection. Consequently, the rate of removal from the blood stream should be a function of particle size. By suitable radioactive labeling, the rate of removal and the tissue distribution of the particles can be measured quantitatively. Also, any change in the removal rate or distribution induced by the incorporation of soluble compounds in the injection formula can be attributed to the added substance.

Two biochemically identical forms of polystyrene latex have been obtained. In one, the polymer species is linear, and in the other, cross-linked (FIGURE 1).

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* Research reported in this paper was supported by the Atomic Energy Commission, Washington, D. C., and the California Division of the American Cancer Society, Inc., New York, N. Y.

† Product of Testagar & Co., Inc., Detroit, Mich.

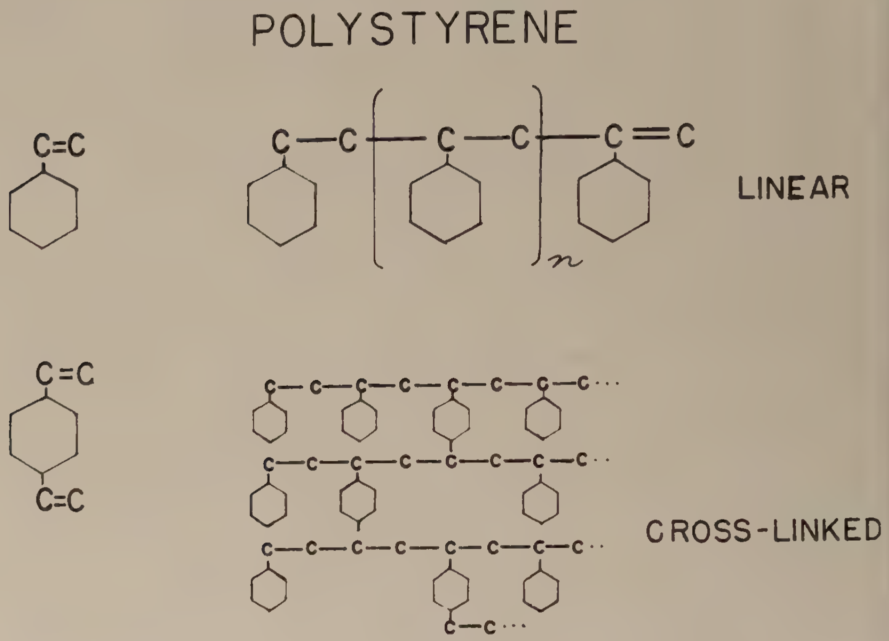

FIGURE 1

Chemically, the forms are different in that the linear form dissolves in organic solvents; the cross-linked form does not. Chemical modifications such as incorporation of iodine can be carried out on the cross-linked form. Prior to the development of techniques for preparing dispersions of cross-linked particles, several samples of linear polystyrene latexes of uniform particle size were obtained* for toxicity evaluation (FIGURE 2). No information was available about their preparation.[2]

Purified samples of latex were injected into the tail veins of 8 mice. Three particle sizes† were used: 1.8 μ, 1.171 μ, and 0.814 μ. The amounts injected ranged from 2.55 to 6.45 mg./gm. body weight. The mice were injected on September 5, 1958, and 7 were alive, healthy, and reproducing on November 20, 1958. One mouse was sacrificed on November 15, 1958, and examined for gross tissue damage; no damage was found.

No reports of the emulsion polymerization of cross-linked polystyrene latexes were found in the literature, and bead polymerization of divinylbenzene apparently is limited to particles larger than 20 μ.[3]

Cross-linked latex is prepared by copolymerizing divinylbenzene with styrene. The cross-linked copolymer was prepared in the colloidal size range apparently for the first time (FIGURE 3). Samples were prepared with estimated average particle sizes of 14 μ, 5 μ, 2 μ, 1 μ, and 0.5 μ. Also, dispersions were prepared with particles smaller than the resolution of optical microscopy.

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* From the Dow Chemical Company, Midland, Mich.

† Average particle diameters as measured by the Dow Chemical Company.

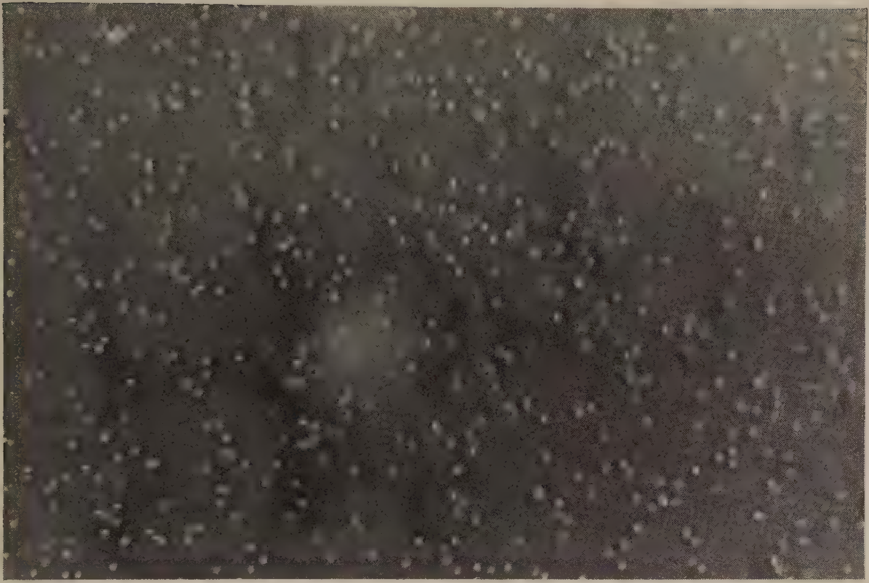

FIGURE 2. Dow linear polystyrene latex. Average particle size, 0.814 μ.

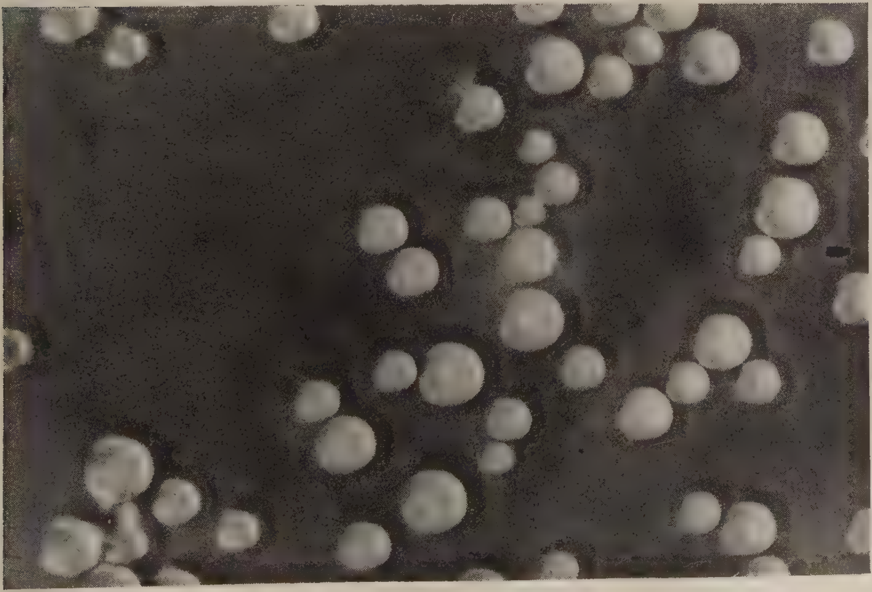

FIGURE 3. Cross-linked polystyrene latex. Average particle size, 14 μ.

The principal feature of the dispersions under development for injection studies is the control of particle size that has been achieved by the proper selection of chemical and physical conditions during polymerization. Experiments are under way to render the new technique consistently reproducible.

Samples of cross-linked polystyrene particles have been iodinated to an average of 10 per cent iodine by weight in the product. Iodine was diffused into the polymer from dichloromethane solution and fixed by reaction with nitric acid in acetic acid. This technique was developed for the incorporation of radioactive iodine as a tracer for physiological experiments. However, a high concentration of ordinary iodine will render the material sufficiently opaque for radiographic evaluation of tissue localization.

Phosphonation and sulfonation of the polymer particles have produced ion-exchange resins. Loading of resins with ions of heavy metals should lead to very opaque model contrast agents. Most promising, however, is the planned use of such resins as intracellular sustained release agents for drug or isotope administration in diseases accessible through the reticuloendothelial system.

Tetraiodophthalic Anhydride Derivatives

Tetraiodophthalic anhydride (FIGURE 4) was chosen as the starting point for a series of derivatives of possible value as colloidal contrast agents. The compound contains 78 per cent iodine by weight, bound to an aromatic ring. The reactivity of the anhydride group permits the selection of many derivatives for synthesis. Derivatives with ester or amide linkages have a point suited to biochemical attack for hydrolysis into soluble fragments. The tetraiodophthalate fragment is relatively nontoxic.[4]

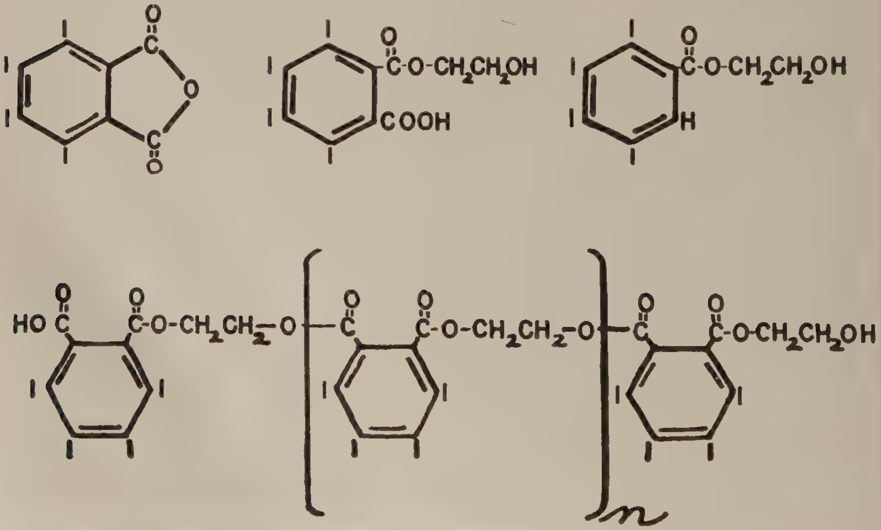

FIGURE 4. Structure of tetraiodophthalic anhydride, hydroxyethyl tetraiodophthalate, hydroxyethyl tetraiodobenzoate, and poly(hydroxyethyl tetraiodophthalate).

Precipitation of tetraiodophthalic anhydride derivatives in water from an acetone solution was chosen as a simple test of dispersibility. Some control over the stability and particle size of the dispersion was achieved by varying the concentration, temperature, and agitation, and by the addition of surfactants and molecular colloids. The initial dispersion was evaporated under reduced pressure to a final concentration of about 25 per cent solid, equivalent to about 200 mg. of iodine per milliliter of dispersion. The stability of this final dispersion, measured as the time required for complete settling, was the criterion for evaluating the potential usefulness of various derivatives that were synthesized. The following compounds gave coarse, unstable precipitates: ethyl, butyl, hydroxyethyl, and hydroxypropyl tetraiodophthalates; phenyl tetraiodophthalimide; acetyl derivatives of tetraiodophenolphthalein (Iodeikon*) and its isomer (Isoiodeikon*). Hydroxyethyl tetraiodophthalate was unique in that the precipitate was a thick gel. None of these compounds appeared promising as a possible colloidal contrast agent.

A possibility that was briefly explored was the precipitation of the zirconyl salt of tetraiodophthalic acid, based on the radiopacity and low toxicity of zirconium. The addition of zirconyl chloride to sodium tetraiodophthalate gave a stable, insoluble precipitate of submicroscopic particles.[5] However, the precipitate was stable only in acidic media, and rapidly hydrolyzed upon neutralization. The acidic dispersion injected into rats was quickly fatal.

The principal effort was directed toward the synthesis of a polyester from tetraiodophthalic anhydride and a glycol.[5] Hydroxyethyl tetraiodophthalate, the half ester prepared by heating the anhydride in ethylene glycol, was refluxed in dimethylformamide. The product of the reaction was a low melting point, acetone-soluble, water-insoluble resin. A crystalline solid was isolated from this resin and identified as hydroxyethyl tetraiodobenzoate, formed by thermal decarboxylation of the half ester. A similar reaction occurred with the propylene glycol half ester. Attempts to identify the polyester possibly formed in this reaction will be made on the uncrystallized resin remaining after recovery of the crystalline solid.

A striking and unique property of both the crystalline and the resinous products was the stable and uniform dispersion that resulted from addition of the acetone solution to water. A series of experiments with various surfactants and molecular colloids in the dispersion media was undertaken to improve stability. Lecithin† and a nonionic surfactant (Pluronic F68‡) were the only compounds tested that conferred stability on the dispersion beyond the untreated control. The best dispersions were stable for about 1 week at room temperature. Under the microscope, the preparation appeared as a uniform dispersion of spherical particles (about 0.8 μ in diameter) in rapid Brownian motion. Much of the material was below the resolution of the microscope.

Animal experimentation with injections of this dispersion have been inconclusive. Small amounts of dispersion (0.9 mg./gm. body weight) were tolerated by mice, but amounts sufficient to give possible opacification of the liver and spleen (2.3 mg./gm.) were immediately fatal. During several injections of mice, material was trapped in the tail and detected radiographically. Within 12 hours this deposit had disappeared from the tail; the mice survived. This suggested metabolic breakdown of the compound. A sample of the dispersion was mixed with 25 times its volume of human blood serum and placed with a blank serum control. Comparison of the light transmission of the mixed sample to the control was made by setting the control at 100 per cent transmission at 5500 Å and recording the change in relative transmission of the mixture. During 24 hours, the relative transmission of the mixture increased from 30 per cent to 80 per cent without observable sedimentation. From this evidence the inference was made that hydroxyethyltetraiodobenzoate underwent fairly rapid metabolic breakdown. A sample of the dispersion was mixed with fresh whole blood and observed under the microscope; no reaction was observed between the particles and the red blood cells.

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* Product of Mallinckrodt Chemical Works, St. Louis, Mo.

† The alcohol-soluble fraction, product of the Glidden Company, Chicago, Ill.

‡ Product of Wyandotte Chemicals Corp., Wyandotte, Mich.

Samples of the dispersion were placed in plastic containers and compared to samples of Lipiodol* containing the same weight of iodine. The radiographic opacifications were identical.

Summary

The initial steps toward the development of a colloidal hepatolienography contrast agent have been described.

Polystyrene particles have been proposed as a physical model for studying phagocytosis.

Iodination of cross-linked polystyrene has been accomplished.

Readily dispersable derivatives of tetraiodophthalic anhydride have been synthesized for study as possible hepatolienography contrast agents.

The continuation of these experiments may lead to the solution of the hepatolienography problem, and may also indicate a quantitative technique for basic exploration of phagocytosis by the reticuloendothelial system.[6]

Acknowledgment

We thank J. W. Vanderhoff, Physical Research Laboratory, Dow Chemical Company, for a generous supply of uniform-size latex samples.

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* Product of Fougera & Co., Inc., New York, N. Y.

LYMPHANGIOGRAPHY AND LYMPHADENOGRAPHY WITH VARIOUS CONTRAST AGENTS*

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Visualization of lymphatic structures by radiographic means can be divided arbitrarily according to the 2 objectives: visualization of lymph trunks and visualization of the lymph nodes. Lymphangiography was established as a clinical procedure mainly by the work of Kinmonth in 1955.[1] Various attempts had been made previously to visualize radiographically the lymphatic structure but, for living subjects, contrast materials utilized were toxic, or the techniques suitable for demonstration in cadavers and animals were not practical for the human.

Kinmonth and others since then have interested themselves mainly in the lymph trunks, rather than in the nodes.[2, 3] Exceptions are Brunn and Engeset[4] and Zheutlin and Shanbrom,[5] who injected enlarged nodes of lymphoma percutaneously in man to show enlargement of regional nodes, and Tjernberg,[6] who performed direct lymphography in animals to compare contrast agents and to detect node enlargements from induced inflammation or tumor.

There are two techniques available for contrast visualization of the lymph nodes; indirect lymphography and direct lymphography. Indirect lymphography consists of injecting the contrast material interstitially and allowing it to flow into the finer lymph vessels; from these vessels it is transported to the larger lymph trunks and nodes. Entrance of opaque material into the lymph system is largely dependent upon rupture of many fine lymphatic vessels by the injection procedure. Some of the contrast material may cross the intact lymphatic wall and some may be transported into the lymphatic system by being ingested by phagocytes that then enter the lymphatic system. With indirect lymphography, lymphograms of inferior quality are often obtained of the lymph structures near the site of injection, while lymph-trunk structures, more distantly located, are very poorly visualized. The effect of the injected contrast materials upon the injection site is not innocuous. When water-soluble, absorbable organic iodides are injected, acute tissue damage may result; when colloidal material is injected, much of it remains at the site of injection.

Direct lymphography, the injection of the contrast material into a large lymph trunk, is capable of producing good lymphograms of nodes and trunks adjacent to and distant from the site of injection. The production of consistently satisfactory lymphograms was found to depend upon the fulfillment of certain optimum technical conditions and to be dependent upon the use of a contrast agent with certain characteristics. Three general types of contrast material were examined in more than 125 separate lymphograms in the dog: water-soluble organic iodides (Diodrast 35 per cent, Urokon 50 per cent, and

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* This investigation was supported, in part, by The James Picker Foundation, New York, N. Y., on recommendation of the Committee on Radiology, National Academy of Sciences–National Research Council, Washington, D. C.

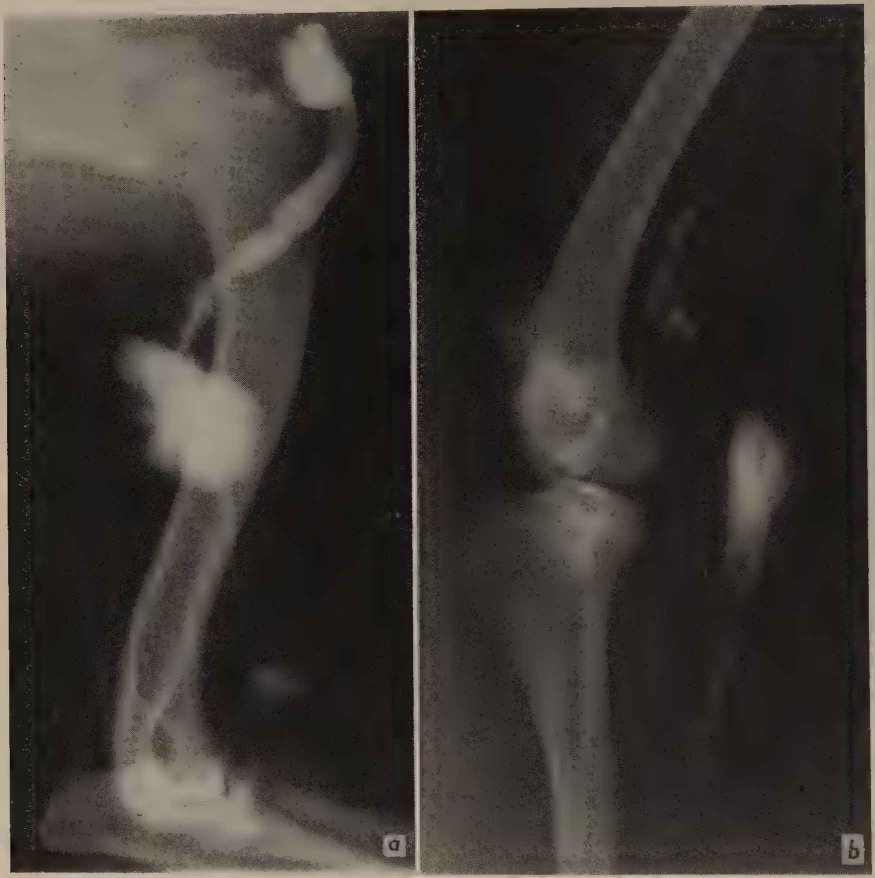

FIGURE 1. Lymphograms of (*a*) the dog's upper extremity with 50 per cent Urokon, and (*b*) of the lower extremity with 52 per cent Cholografin, showing diffusion of the water-soluble iodides through the lymph trunks and nodes, obscuring details of the lymph structures.

Cholografin 52 per cent); fatty materials (Ethiodol and Angiopaque); and particulate materials (Thorotrast and stannic oxide).

The rapid diffusion of water-soluble iodies through the lymphatic trunk and through the structures of the lymph nodes was a distinct disadvantage. FIGURE 1 illustrates this with Urokon injected into the lymph trunks of the upper extremities of the dog, and Cholografin in the lymph trunk of the lower extremity of the dog. This escape of contrast material from the lymph trunk in some cases may be due to actual rupture of the trunk, but in most cases to diffusion of the material from the intact wall. Tjernberg[6] examined several agents and considered Cholografin the least diffusible.

The diffusion of water-soluble contrast materials may depend in part upon the injection pressure. Since one of the primary purposes of lymphography would be to show obstructed lymph channels, a contrast material that passes

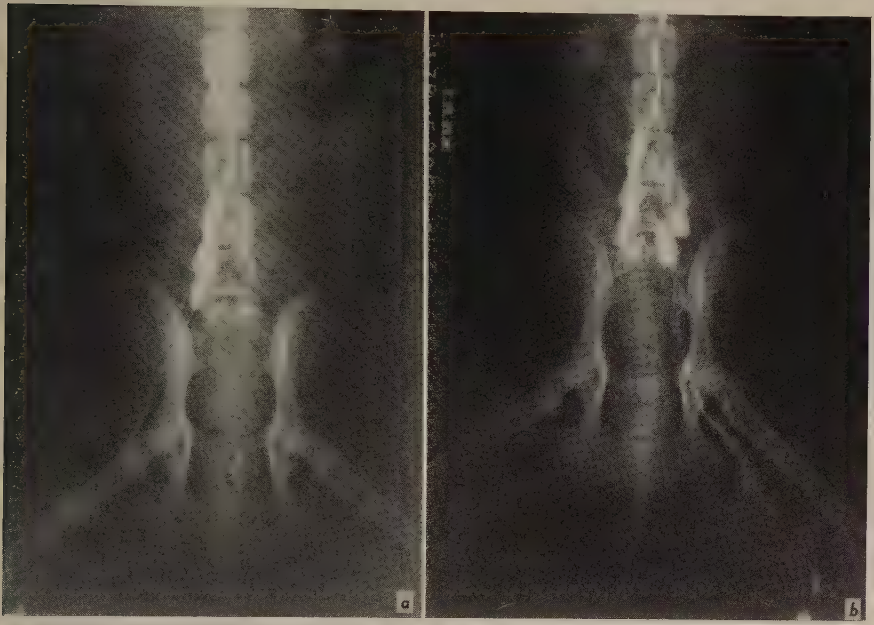

FIGURE 2. Lymphograms of dog's iliopelvic nodes and lymph trunks. (*a*) Normal unobstructed side. (*b*) Lymph trunks on side that previously had been ligated surgically. Note collateral lymph circulation, visualization of contralateral nodes, as well as obstruction to normal upward flow of lymph.

out of the lymph trunk when pressure within the lumen increases (as a result of obstruction) would certainly not be desirable. Escape of particulate contrast materials or fatty contrast materials through the lymph trunk was observed only rarely (FIGURE 2).

Fatty substances were found to be unsatisfactory in two respects: the mixing of Ethiodol with the lymph resulted in the breaking up of the material into small globules, which sometimes gave a confusing picture, and (also with Ethiodol) pulmonary embolization of fat globules occurred.

The viscosity of the contrast material is important, whether direct lymphography is accomplished by injecting contrast agents through a very fine needle (No. 30) or through a small polyethylene catheter (No. P.E. 10). In either instance, with high viscosity, the actual injection is most difficult. TABLE 1 lists the measured flow times of the various contrast materials through an Ostwald tube at 37° C. in a constant-temperature water bath. Not only is there difficulty in injection through the external apparatus, but the fineness of the lymph trunks and lymph channels within the nodes makes a free-flowing, low-viscosity preparation essential.

To explore the clinical possibilities of lymphography, lesions similar to those suspected in metastatic neoplasm were produced within the nodes. In one group of animals a small abscess was produced in a lymph node by an electrocautery needle; in another group, a small polyethylene ball was implanted in

TABLE 1

COMPARISON OF VISCOSITIES

Agent	Flow time (Ostwald viscometer), sec.	Relative viscosity
Distilled water	90	1.00
Diodrast 35%	247	1.91
Urokon 50%	206	2.92
Cholografin 52%	506	7.19
Angiopaque	607	7.57
Ethiodol	2454	34.20
Thorotrast	768	11.10
Stannic oxide	350	4.66

the node. After allowing a suitable period for healing of wounds, lymphography was performed with the various contrast materials. Thorotrast was found best for visualization of the abscess lesion (FIGURE 3). Stannic oxide suspensions gave poorer results. This was thought to be due to the larger particles and irregularity of particle size in the stannic oxide suspension.

Water-soluble materials diffused through the inflammatory and necrotic tissue as well as through the normal tissue and did not show lymph node detail. Actually, abscess lesions were concealed by water-soluble agents (FIGURE 4). Water-soluble agents, fatty materials, and particulate materials were all capable of showing the embedded polyethylene ball as a negative-filling defect (FIGURE 3). Although actual metastatic neoplasm in the lymph nodes of the dog could not be obtained, the simulated lesions were thought to represent metastases sufficiently well for the purposes of this experiment.

Metastatic neoplasm in the lymph nodes has no lymphatic channels of its own and, except in rare instances, is not phagocytic. Therefore, a sterile abscess or polyethylene ball that replaces or displaces normal cells of the lymph nodes would be expected to show as a negative-filling defect in contrast radiography. Nonpenetration of colloidal or fatty materials into a metastatic deposit and absence of phagocytosis of colloidal material by a metastatic deposit would be expected, but we cannot predict that water-soluble materials would not permeate the tumor tissue within the node and thereby conceal it. For this reason, the abscess composed of living and nonliving tissue may more nearly approximate a metastatic deposit. This is not an all-important point, since both lesions were utilized only to begin exploration of techniques for visualizing metastases; further work with actual neoplasms will be necessary for clarification.

The direct injection of colloidal or particulate material into the lymphatic structures could serve as a functional test in that the phagocytic capacities of the lymph cells may be altered by pathological processes, which could then be demonstrated by the abnormal uptake or abnormal retention of the colloidal material. This is illustrated in FIGURE 5*a*, in which the filling of the node by Thorotrast is noted. FIGURE 5*b* shows retention of opaque particles in the macrophages around an abscess after flush of saline solution through the lymph trunks and nodes. Possibly, lymphomas may be manifested early by a change in phagocytic capacities; this should be investigated. An important point,

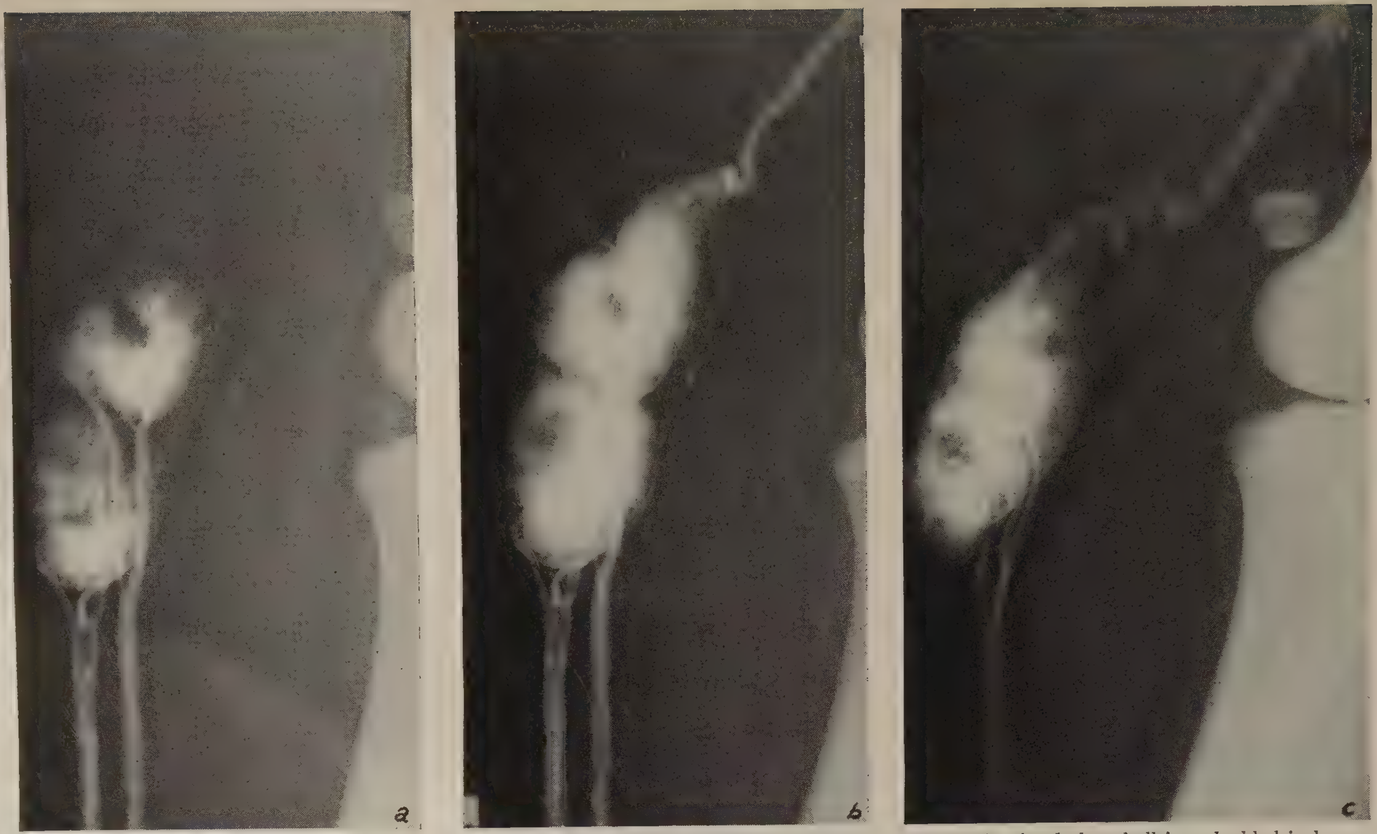

FIGURE 3. (*a*, *b*) Lymphogram of popliteal nodes in dog. Cautery lesion is in upper node, and polyethylene ball is embedded in lower node (Thorotrast). (*c*) Cautery lesion in upper pole of node; polyethylene ball in lower part (stannic oxide suspensions).

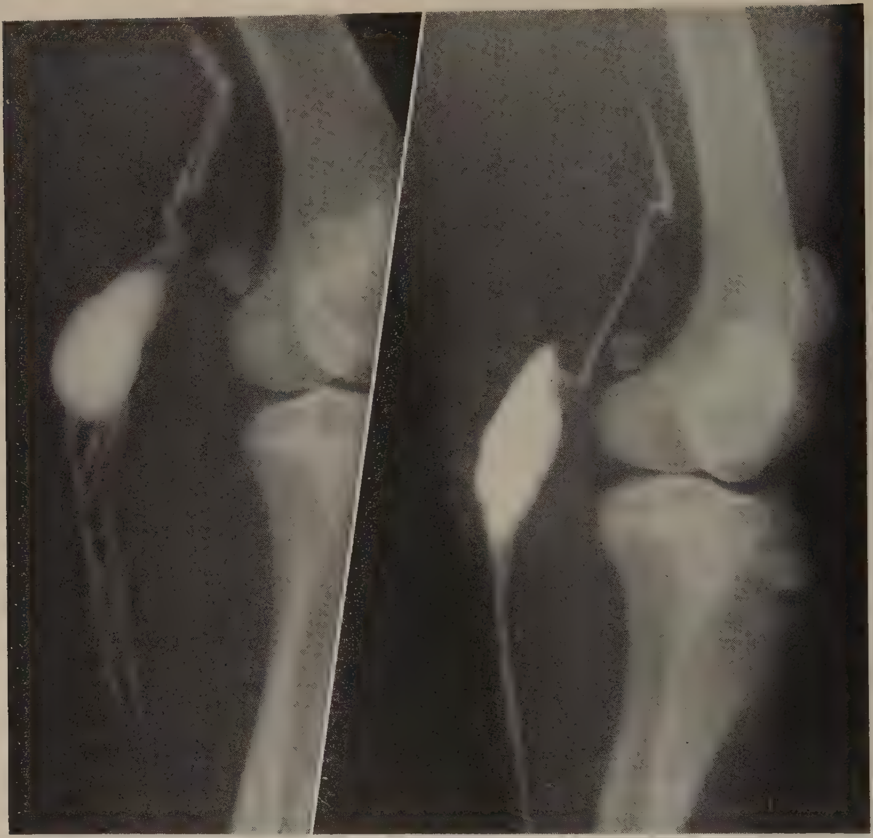

FIGURE 4. Diffusion of water-soluble contrast agent within two nodes conceals rather than demonstrates previously produced cautery lesions. Compare to FIGURE 3.

which should be applicable to clinical lymphography, is the necessity for selecting a distal lymph trunk for injection. A trunk sufficiently distal on the limb is advised for injection of the inguinal-pelvic nodes in man. Selection of a trunk close to a regional node group may result in contrast material bypassing some of the nodes. Serial-film examination of a lymph system done while increments of contrast material enter the system is advised. Partial filling of a node does not allow evaluation of a node's normality.

Histological studies performed in conjunction with radiographic studies by George Zimmerman, Department of Pathology, State University of Iowa College of Medicine, revealed that there was no adverse node response to direct lymphography with water-soluble organic iodides, Thorotrast, and stannic oxide. The condemnation of Thorotrast on the basis of its radioactivity is already well known. It must be realized that our studies were relatively short-term, and in this period no tissue damage (as reported in long-term studies) was observed. Foreign-body reaction was noted about retained

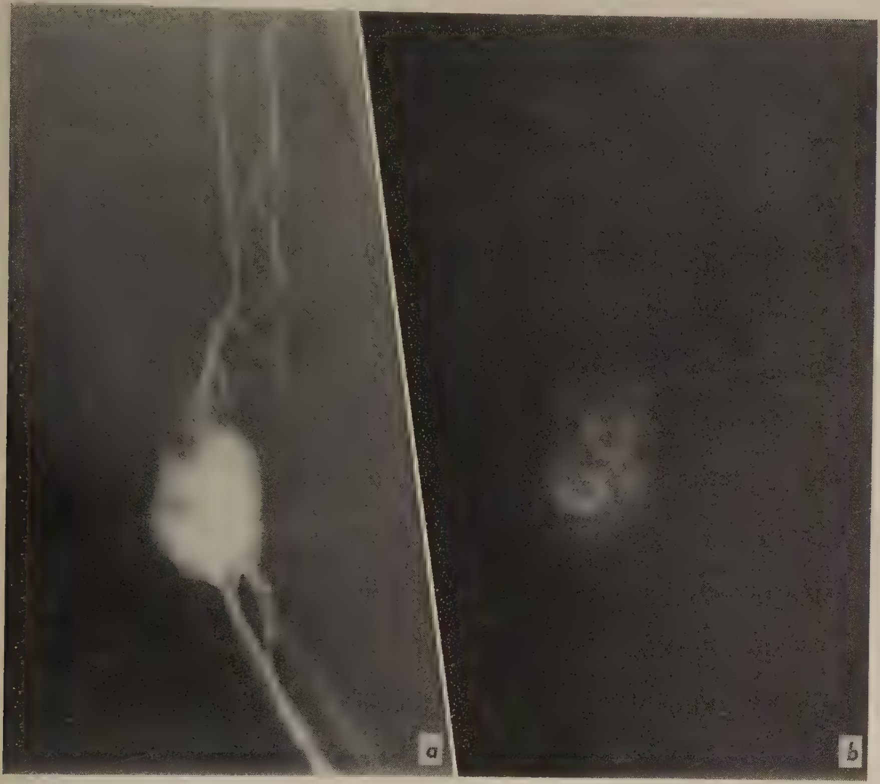

FIGURE 5. Lymphogram showing (*a*) two cautery lesions in a dog's popliteal node, visualized as negative-filling defects. (*b*) After flush of saline solution through the node, opaque particles of contrast material are retained in the phagocytes surrounding the lesions, while the more normal tissue does not retain the particles. The use of particulate contrast material (Thorotrast) may serve as a functional test in this manner.

globules of Ethiodol, and foreign-body reaction and necrosis were noted about retained particles of Angiopaque.*

A contrast material should give more than fleeting visualization of lymph structures. Ethiodol, Angiopaque, Thorotrast, and stannic oxide were retained sufficiently long in the nodes and trunks to make possible the production of radiographs at leisure, and with variations in technique when necessary. The rapid-diffusing contrast agents did not allow unhurried or repeated filming; at best, clearness of detail was sacrificed and, at worst, obscuration of the area occurred. The nonwater-soluble materials could be flushed to various degrees from the visualized nodes and trunks by subsequent injections of saline solution. It was not necessary to remove the water-soluble materials by flushing, since tissue-absorptive processes effected their removal.

The question should be raised whether it is desirable to visualize nodes only temporarily. If nodes were visualized for long intervals by retention of the radiopaque materials in their cells, displacement or replacement of lymph structures by recurrent neoplasm might be detected in the posttreatment period of malignancies. Long-term node visualization would be dependent

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* Since Angiopaque is no longer commercially supplied, the preparation used in these experiments is an outdated one.

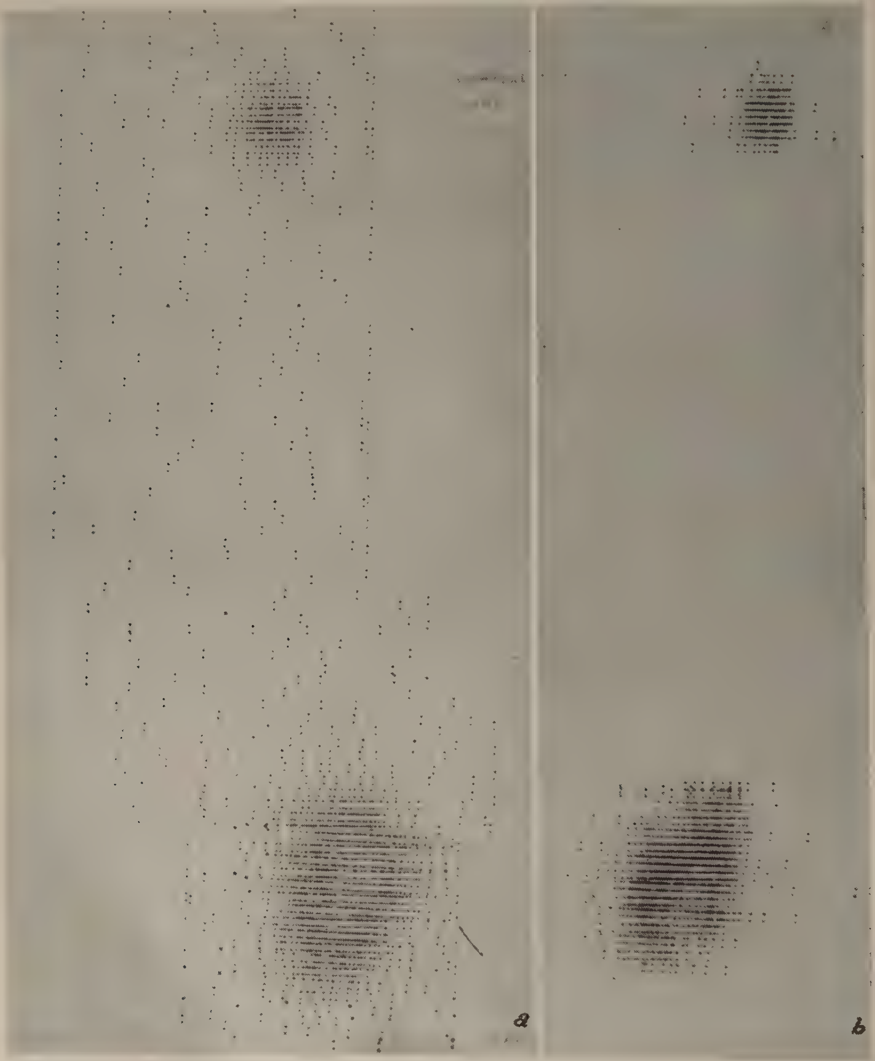

FIGURE 6. (*a*) Scintigram of dog's hind leg 30 min. after injection of 250 μc. of radioactive colloidal gold into the tissues of the foot pad. (*b*) Scintigram 5 days after injection. Note large amount of radioactivity in foot pad (lower area of activity on scintigram) and popliteal node area (upper area of activity on scintigram) at both 30 min. and 5 days and, especially, the long undesirable retention of radioactivity in the foot when the intention is to irradiate the node. When the injection of radioactive colloid is made directly into the lymph trunk, only the node is irradiated.

upon the utilization of a contrast material that is completely noninjurious to all tissues with which it comes into contact and noninjurious to tissues that are exposed to its end products of metabolism. A slowly metabolized contrast agent or a completely inert contrast agent, as preliminary evidence shows stannic oxide to be,[7] may then be the preferred type of agent. The feasibility of long retention of any compound within the nodes is in doubt; it would be necessary for contrast material to be within the nodal cells, but these cells may not remain in the node. If contrast materials are removed from the nodes by saline flushing or by later discharge of materials from the cells, their effect on tissues at the site of eventual deposition must be considered. Materials so removed from the lymphatics normally enter the systemic circulation by the thoracic duct. If particles are large, multiple small pulmonary emboli result; if particles are not filtered off as emboli, they are ingested from the circulating blood by the phagocytic cells of the liver, spleen, and bone marrow. The effect of long-term tissue toxicity would be similar to that produced by contrast materials injected intravenously.

Although this paper is devoted largely to radiodiagnostic subjects, the therapeutic implications of lymphography techniques should be considered. By utilizing the same technique as in direct diagnostic lymphography, radioactive and chemotherapeutic agents can be transported to the diseased node without more than minimal exposure of intervening tissue. This can be illustrated best by scintigrams following the injection of radioactive colloidal gold into the foot of a dog. FIGURE 6*a* is a scintigram made 30 min. after injection, showing the large amount of activity at the site of injection in the foot, and the activity in the popliteal lymph node. Five days later (FIGURE 6*b*), a large amount of radioactivity remains in the foot and in the lymph node. When the radioactive colloidal gold is injected directly into the lymph trunk, all of the activity is in the node and none is detected in the surrounding tissue.

Addendum

While animal experiments were being performed in this laboratory to determine the likelihood of demonstrating neoplastic involvement of nodes, not only did we become aware of Tjernberg's related experimental work, but the first clinical paper on this problem was published.[8] Collette reports that lymphography can visualize evidence of inguinoileopelvic involvement by pelvic neoplasms when this extension is not suspected or is doubtful on clinical examination; it can also confirm the clinical diagnosis of invasions.

The elements necessary for successful lymphography in the dog seem to hold true for man, in light of our early attempts. These are: a low-viscosity, non- or minimally diffusable, highly radiopaque contrast agent without initial or late toxicity, a distal site of injection, serial films to estimate accurately filling of nodes, and a preference for a particulate contrast material. Lymphography in man is much more difficult, technically speaking but, with experience, we hope to improve our results.

Recently, Hypaque 50 per cent was found to diffuse less than other soluble iodides, to give excellent radiopacity, and to be well tolerated by tissues. Consequently, we prefer this agent in human studies. Its viscosity, although not excessive, is higher than we should like.

A paper by Fischer and Zimmerman,[9] giving more information, has recently been published.

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IOPANOIC ACID

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University Hospital, Ann Arbor, Mich.

A little more than 7 years ago iopanoic acid was made available to us for clinical testing; since that time, we have had occasion to use it in approximately 20,000 cholecystograms. Early in its evaluation, this acid demonstrated its right to be accepted as the cholecystographic medium of choice. It is of interest that in a period of years at a large teaching hospital, the incidence of any particular disease and the types of radiographic examinations (except for those of recent discovery and innovation) do not seem to fluctuate widely. A tabulation of the number of cholecystograms and their findings is shown in TABLE 1 for the last 3 years for which statistics are available.

This variety of clinical material is occasionally a handicap in that it necessitates expeditious, if not hurried, handling of large numbers of patients by limited personnel. However, it also provides adequate opportunity for evaluating various cholecystographic contrast media as they are presented. We shall review briefly the sequence of our studies at the University Hospital in the evaluation of iopanoic acid, or Telepaque, and its dosage for oral cholecystography, and shall dwell at somewhat greater length on two current studies, one recently completed and another recently begun.

One initial feature in the evaluation of any contrast medium is the side effects noted by the patient following administration. It is of interest that considerable variation in the side effects is reported by different observers for various media; obviously, there is a fairly large subjective element in the reporting of signs and symptoms. It is sufficient, I think, to insist that the same observer, or group of observers, conduct the comparative study, preferably without knowing which of two contrast media has been administered, and that the questioning be kept as objective as possible. It is also desirable that a significantly large number of patients be examined in one institution to avoid scattering a limited amount of contrast material in several places. Our early evaluation of Telepaque and its comparison with Priodax, both in 3-gm. dosage, agreed in general with other early reports. Approximately 20 per cent more asymptomatic patients were found with Telepaque (62.5 per cent). Complaints of nausea were reduced from 16.6 to 5.8 per cent, mild diarrhea was reduced from 27 to 22.8 per cent, and severe diarrhea from 6.4 to 2.5 per cent. Dysuria was reduced from 24.4 to 13.7 per cent. Tabulation of quality of visualization gave even more striking results: dense visualization was increased from 20 to 60 per cent, the combination of dense and good visualization increased from 62 to 83 per cent, faint visualization decreased from 21.8 to 7.6 per cent, and nonvisualization decreased from 16.2 to 9.4 per cent. A group of cases in which each patient was studied with both media, demonstrated 68.2 per cent with improved visualization with Telepaque; improved visualization of radiolucent stones was found in 72 per cent of patients having them. An increased incidence of duct visualization with fat feeding was also found.[1]

TABLE 1

UTILIZATION OF CHOLECYSTOGRAPHY

Year	No. of cholecystograms	Visualization			Calculi
		Normal	Faint	None	
1954–1955	3435	2546	259	383	442
1955–1956	3410	2389	337	382	406
1956–1957	3134	2191	377	338	388

It was noted that the gall bladder was sufficiently dense to obscure a radiopaque calculus in one case, and that a considerable amount of granular residue was present in the colon. These observations were thought to be indications that a smaller dose might be advantageous. Accordingly, a large-scale evaluation of a 2-gm. dosage of Telepaque was carried out. Further slight reductions in diarrhea to 17.6 per cent and in dysuria to 7.0 per cent were found, together with an increase from 62.5 to 66.2 per cent in the number of patients without side effects. The extremely dense gall bladder shadows were reduced from 59.6 to 46.6 per cent, with a compensatory increase in the number of good shadows, so that a loss of 3.8 per cent was found in the combined good and excellent shadows. This was more than counterbalanced by the decreased risk of obscuring biliary calculi by the denser shadows of the 3-gm. dose. A trace of residual contrast in the colon continued to serve as satisfactory evidence that the contrast material ingested had progressed as far as the right colon. A sampling of patients according to weight indicated that the 2-gm. dosage was satisfactory for the clinically encountered range of patients' weights. It was then concluded that for established clinical routine the 2-gm. dose was entirely satisfactory.[2]

The introduction of Teridax necessitated a further comparative study, and a 5 per cent increase to 71 per cent in patients without side effects was noted with this newer preparation; the incidence of mild diarrhea was nearly halved, showing an incidence of 9.7 per cent. The degree of visualization of the gall bladder was disappointing, however, with marked reduction in the incidence of dense gall bladder shadows, and with the incidence of faintly and nonvisualized gall bladders more than doubled. It was felt that this outweighed the value of the decrease in side effects and that Telepaque in 2-gm. dosage remained the medium of choice.[3]

Attempts were made to improve Telepaque by acetylation of its molecule, and clinical trial of this material showed an amazing 94 per cent of patients free of side effects, but with a striking increase in faint and nonvisualization to 44.6 per cent.[4]

The intriguing possibility that the fat-free evening meal was less important than it had been because of the later hour (10 P.M.) of ingestion of Telepaque tablets was tested with 50 volunteers. The examination following the fat-free meal excelled that following a fatty evening meal in 56.5 per cent of cases, with 21.7 per cent equally well visualized; the continued use of the fat-free meal was thus justified.[5]

With the continued use of 2 gm. of Telepaque as the dosage and medium of choice, it was felt that evaluation was not complete until a correlation had been made between the cholecystographic results and the surgical pathological findings. An initial study of 124 cases indicated that a high degree of accuracy (99.2 per cent) was achieved in anticipating gall bladder abnormality and that, in general, the more severe inflammatory changes are reflected in the decreased density of the gall bladder shadow, although this could not be rigorously applied to individual cases.[6] However, the topic was one of sufficient interest and difference of opinion (concerning its application in the extension of interpretation of cholecystograms) to justify further exploration with the collaboration of a pathologist.[7] Accordingly, the surgical cholecystectomy material for a 2-year period, July 1956 to July 1958, was utilized. The microscopic pathological material was reviewed by the pathologist and all cases were classified according to the type of pathology present. In addition, cases were designated as I, II, or III to indicate the severity of the inflammatory change in the gall bladder wall. Criteria for the designations were: (1) minimal, few lymphocytes and plasma cells in *substantia propria* in the wall about vessels; (2) moderate, some fibrous scarring and moderate numbers of inflammatory cells throughout the wall; and (3) severe, many inflammatory cells throughout the wall, with marked fibrosis.

The cholecystographic films were reviewed independently by the radiologist, and findings were classified as to degree of visualization: excellent, good, faint, or nonvisualization. The presence or absence of stones was recorded with notations as to their number and character—lucent, opaque, or mixed. The microscopic sections of 274 cases were reviewed. Many had been operated upon after referral, following diagnostic studies elsewhere; these were excluded because the dosage and contrast medium used were not known. Some were subjected to operation on the basis of opaque stones seen by scout filming without cholecystography. Oral cholecystography had not been attempted in cases with acute disorders of the abdomen.

The final collection of patients found to have adequate cholecystographic and pathological data for purposes of correlation numbered 133. These were found to fall into the pathological categories and degrees of inflammatory change shown in TABLE 2. Four cases are duplicated by virtue of showing pathological changes in 2 categories.

The degree of visualization and demonstration of stones was then tabulated for each of the subgroups and their degree of inflammatory change. Stones were present in 132 cases, but were demonstrated in only 90. A composite table was then made to demonstrate the variations of visualization with the degree of inflammatory change (TABLE 3).

It is helpful in our analysis to consider the cases first from the standpoint of visualization; TABLE 3 is thus adapted with percentages of each visualization group (TABLE 4).

The data expressed in this manner yield the following interpretation (with a 2-gm. dosage of Telepaque), after failure of absorption and gross liver damage have been excluded:

TABLE 2

DEGREE OF INFLAMMATORY CHANGE*

Pathology	Severity of change		
	I	II	III
Acute cholecystitis	—	—	—
Acute exacerbation of chronic	—	1	1
Subacute	4	3	1
Chronic:			
Nonspecific	61	16	2
Proliferative	—	2	—
Productive	4	9	2
Lipogranuloma	—	1	2
Calcific	—	1	2
Hydrops	1	1	—
Cholesterolosis	12	1	—
Lymphofollicular		3	4

* Figures represent number of cases.

TABLE 3

INFLAMMATORY CHANGE*

Visualization	Severity of change			Ca (2)
	I (85)	II (40)	III (6)	
Excellent (4)	4	—	—	—
Good (52)	47	5	—	—
Faint (29)	21	7	1	—
Nonvisualization (48)	13	28	5	2

* Figures represent number of cases.

TABLE 4

INFLAMMATORY CHANGE*

Visualization	Severity of change			Ca
	I	II	III	
Excellent	100	—	—	—
Good	90.4	9.6	—	—
Faint	72.5	24.2	3.3	—
Nonvisualization	27.2	58.3	10.3	4.2

* Figures represent percentages of total cases in each category.

(1) All gall bladders that give excellent visualization in the presence of stones show only minimal inflammatory changes in the surgical specimen.

(2) Ninety per cent of gall bladders giving good visualization in the presence of stones will show only minimal inflammatory changes, with approximately 10 per cent showing moderate inflammatory change, and none showing severe changes.

(3) Gall bladders showing faint visualization in the presence of stones, or in which visualization is so faint that stones cannot be definitely established or

TABLE 5
INFLAMMATORY CHANGE*

Visualization	Severity of change			Ca
	I	II	III	
Excellent	4.7	—	—	—
Good	55.3	12.5	—	—
Faint	24.7	17.5	16.7	—
Nonvisualization	15.3	70.0	83.3	100

* Figures are percentages of total cases in each category of inflammatory change.

excluded, will show a large proportion of cases with only minimal change, about one-fourth with moderate change, and an occasional case with severe changes.

(4) Cases with nonvisualization may have minimal changes in the gall bladder wall, are most likely (58.5 per cent) to have moderate inflammatory changes, and may have severe inflammatory changes or neoplasms.

(5) The two carcinomas of the gall bladder in this series had nonvisualization of the gall bladder.

It is helpful to express the data on visualization charted against inflammatory changes as percentages of the total number showing various degrees of inflammatory change (TABLE 5). The following interpretations may then be made from this arrangement of the data:

(1) All cases of severe inflammatory involvement of the gall bladder wall had either faint or nonvisualization.

(2) Seventy per cent of cases with moderate inflammatory changes in the gall bladder wall in the presence of stones had nonvisualization of the gall bladder, and more than half the remaining 30 per cent had faint visualization.

(3) Cases showing minimal inflammatory changes in the presence of stones may present any density of the gall bladder shadow, with a few excellent, the majority good, about one-fourth faint, and 15 per cent nonvisualization.

It is of further interest to consider the individual subtypes of chronic cholecystitis. As can be seen from TABLE 1, the subgrouping into individual classes of pathological types makes many small groups except for the chronic nonspecific, productive, and cholesterolosis groups. Individual analysis of these groups is shown in TABLE 6. Thus, in this subgroup, severe inflammatory

TABLE 6
CHRONIC NONSPECIFIC CHOLECYSTITIS*

Visualization	Severity of change		
	I	II	III
Excellent	4	—	—
Good	36	2	—
Faint	12	3	—
Nonvisualization	9	11	2

* Figures represent number of cases.

TABLE 7
CHRONIC PRODUCTIVE GROUP

Visualization	Severity of change		
	I	II	III
Excellent	—	—	—
Good	1	—	—
Faint	1	—	1
Nonvisualization	2	9	1

TABLE 8
CHOLESTEROLOSIS GROUP

Visualization	Severity of change		
	I	II	III
Excellent	—	—	—
Good	8	—	—
Faint	3	—	—
Nonvisualization	1	1	—

change leads to nonvisualization, moderate change gives nonvisualization predominantly, with a few faint and good; minimal change gives a variety of visualizations, the largest number classified as good.

Similar evaluation of the chronic productive group is shown in TABLE 7. This would suggest that chronic productive change is more apt to produce a decrease in the density of the gall bladder shadow than similar degrees of chronic nonspecific change.

Analysis of the cholesterolosis group, shown in TABLE 8, suggests that cholesterolosis as seen in these specimens is accompanied by minimal inflammatory change and retains predominantly good visualization in the presence of stones.

Having made the analysis of the correlation of gall bladder inflammatory change and the density of its roentgen visualization, we consider the question of the practical value of this background of information to our daily interpretation of cholecystograms. We divide our conclusions into two groups, the first directly related to the data analyzed here, the second a projection of these findings to cases without stones.

The following conclusions may be stated with considerable certainty for cases in which 2 gm. of Telepaque is used and where failure of absorption and gross liver damage are excluded:

(1) A gall bladder with excellent visualization in the presence of stones has only minimal inflammatory changes in its wall.

(2) No gall bladder giving good visualization in the presence of stones will have severe inflammatory change, and 90 per cent will have only minimal inflammatory changes.

(3) Faint visualization in the presence of stones may be associated with any degree of inflammatory change, but an increased incidence of moderate and severe changes will be associated with faint visualization.

(4) Cases of nonvisualization on oral cholecystography with opaque stones or with lucent stones subsequently demonstrated by multiple oral or intravenous doses of medium are most likely to have moderate or severe inflammatory changes.

It must be remembered that the actual number of cases in which it is possible to carry out such correlative studies is extremely small in comparison with the total number of cholecystograms done. For example, the 133 cases subjected to analysis here were the only ones with complete cholecystographic and pathological data for a period in which more than 6000 cholecystograms were done. They represent a highly selected group with sufficiently convincing clinical history and roentgen findings to persuade the surgeon to remove the gall bladder. The accuracy of the prediction of gall bladder abnormality is not surprising when one remembers that the roentgen findings play a role in the selection of patients for surgery.

Projection of these findings of some correlation of the inflammatory changes and density of gall bladder shadow to cases without stones is therefore hazardous, but we think the following conclusions are justified, again with the use of 2 gm. of Telepaque and with failure of absorption and gross decrease in liver function excluded:

(1) Excellent and good visualization of the gall bladder does not exclude minimal chronic cholecystitis.

(2) Faint visualization on repeated examination is suggestive of chronic inflammatory disease, which may be of varying degree. The determination whether this constitutes a surgical indication does not lie with the radiologist but, rather, presents a problem for clinical evaluation, additional investigation, and surgical judgment. Stones may be demonstrated with additional higher doses of oral medium or with intravenous medium. Cases that come to surgery with sufficiently faint visualization to preclude the evaluation of lucent stones and in which additional media add no information have been found to have both stones and chronic inflammatory disease.

(3) Cases that come to surgery with nonvisualization of the gall bladder on repeated examination and in which no information was added by increased dosage or intravenous medium have had both stones and chronic inflammatory disease.

(4) In cases with nonvisualization of the gall bladder and in which subsequent increased oral dose or intravenous studies add no information, neoplasm of the gall bladder cannot be excluded without direct surgical evaluation.

To summarize the preceding portion of the discussion briefly, additional data have been obtained correlating the density of visualization of the gall bladder shadow (obtained by oral cholecystography with 2 gm. Telepaque) with the histopathological changes in the gall bladder; some possibilities and limitations to be applied in the interpretation of future cholecystograms with this same medium and dosage also have been suggested. When evaluating a new cholecystographic medium or variations in dosage of one in use, it should be remembered that variations in media and dosage can influence the density of the gall bladder shadow. In order to derive the most information from the cholecystogram it is both possible and desirable to adjust the dosage so that a broad spectrum of visualization is found in cases of varying severity of inflammation. A correlation of the density of the gall bladder shadow with the inflammatory changes seen in the surgical specimen gives us the basis for a more complete interpretation of cholecystograms with which we may be confronted.

The last phase of the discussion of continuing use and study of Telepaque relates to the study of its efficacy in relation to newer preparations that are offered for clinical trial. For the most objective evaluation of any two contrast media that are compared, it is desirable for the physician who interviews the patient concerning side effects to have no knowledge of which preparation was administered; this is also desirable with respect to the radiologist who interprets the films. Only in this way can the objective advantages of the "double-blind" trial be maintained. This ideal approach has been difficult to maintain in the past because of the attachment of floor nurses to established routine, and their practice of accumulating caches of contrast material for borrowing from and lending to other nurses. Hence it has occasionally been more convenient to shift an entire hospital from one preparation to another rather than to risk confusion among twenty nursing stations by an elaborate double-blind administration. For more recent studies, however, we have been able to achieve objectivity by dispensing one medium to inpatients and another to outpatients. Since outpatients don hospital gowns for their fluoroscopy and filming, their identity is not readily apparent to the fluoroscopist who, prior to obtaining spot films in the upright position with whatever rotation and pressure seem advisable, interviews the mixed group of inpatients and outpatients concerning side effects. Similarly, groups of films are gathered with a mixture of inpatients and outpatients, so that the film reader does not know the identity of the contrast medium until after he has recorded his observations. One difficulty with this arrangement is that the inpatient cholecystograms are greater in number and are more apt to have pathology. This is taken into account by changing the preparations midway through the study so that each preparation is used in comparable groups of inpatients and outpatients; the alternation of media continues throughout the study so that the interviewing fluoroscopist and the film interpreter remain unaware of the exact medium used as they confront patient and film.

The program for obtaining an objective comparison of two cholecystographic media is now under way, using the newly introduced Orabilex (Fougera) in 4.5-gm. dosage with our standard Telepaque dosage of 2 gm. Orabilex is a triiodinated compound 3(3-butyrylamino-2,4,6-triiodophenyl)-2-ethyl sodium acrylate containing 57 per cent iodine. In its first clinical trials it was used in 6-gm. dosage, but it is currently administered in 6 capsules of 0.75 gm. each. Its comparison with Telepaque is only in the early stages of study at our institution. The following data are presented only as a preliminary progress report and to illustrate the application of a double-blind evaluation on a large scale. A final definitive evaluation of course, is withheld pending completion of the study.[8]

The comparative evaluation of side effects in the first month of administra-

TABLE 9

SIDE EFFECTS*

	Orabilex (150 cases)	Telepaque (85 cases)
None	82.7	62.4
Nausea	10.0	7.0
Vomiting	1.3	1.2
Diarrhea	2.7	23.6
Dysuria	2.7	3.5
Cramps	3.3	13.0
Other	5.3	7.0

* Figures are percentages of total.

TABLE 10

DEGREE OF VISUALIZATION WITH TWO DIFFERENT MEDIA*

Visualization	Orabilex (150 cases)		Telepaque (85 cases)	
Excellent	21.4	74.0	3.5	76.5
Good	52.6		73.0	
Faint	13.3	26.0	20.0	23.5
Nonvisualization	12.7		3.5	

* Figures are percentages of total cases.

tion of Telepaque (2 gm.) to outpatients and of Orabilex (4.5 gm.) to inpatients is summarized as in TABLE 9.

Among the "other" side effects with Orabilex are 2 cases of heartburn, 3 of flatulence, 1 of after-taste, 1 of mild urticaria in a patient with an allergic history, and 1 of headache. Among the other side effects tabulated with Telepaque in this series were 2 cases of heartburn, 1 of headache, and 1 of urticaria. It is noted that there are some minor variations in Telepaque side effects in comparison with the previous series of 500 cases; these differences may diminish as a larger number of cases is attained. Similarly, the side effects of Orabilex may show additional slight variations in percentages as the 500 mark is approached.

Preliminary tabulation of the degree of gall bladder visualization attained with the 2 media is shown in TABLE 10. Again, we stress the fact that these tentative totals may change when the 500 goal is achieved, with comparable groups of patients administered each medium. It can be stated roughly, for the present, that the totals of excellent and good visualization are roughly comparable, as are the totals of faint and nonvisualization, Orabilex showing higher incidence at the extremes. Any further analysis does not appear to be desirable at this time because of the limited data, and final judgement is suspended until completion of the entire study, with evaluation of visualization of stones and ducts, variations in dosage, and operative findings. It may be tentatively stated, however, that Orabilex appears to offer some reduction in side effects while maintaining roughly comparable satisfactory visualization of the gall bladder, and that further intensive comparative study with Telepaque is warranted.

We have tried to summarize briefly our experience with iopanoic acid, or Telepaque, from its initial comparative study with the previously widely used iodoalphionic acid, the evaluation of variation in its dosage, and its establishment at 2-gm. dosage as our medium and dosage of choice for oral cholecystography. Evaluation of variations in its chemical structure and comparison with other media as they have become available in the past few years have been completed. The possibilities and limitations of interpretation of gall bladder density with reference to the extent of underlying inflammatory changes have been outlined on the basis of pathological findings in cases operated on after roentgen study with 2-gm. dosage. Finally, the mechanism for setting up a valid, objective, double-blind study of a large number of cases for comparison of two media has been described and an early progress report of such a study has been presented.

Iopanoic acid has enabled us to take one of the giant steps forward in oral cholecystography, has served us well as the medium of choice since its introduction, and will be the standard of reference for newer media as they are evaluated.

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TWO-PHASE OPACIFICATION OF THE LIVER IN CIRRHOSIS*

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Among the various methods of roentgen opacification of the liver, that employing injection of an opaque medium in aqueous solution into the sinusoids of the splenic pulp has been used most successfully. Following such injection it has been possible by means of serial splenic portography to visualize the liver in two major phases. The vasculogram phase consists of visualization of the intrahepatic portal vein branches, principally those of the right main branch; the second phase, termed the hepatogram, represents a diffuse homogeneous opacification of liver normally, probably due to filling of hepatic sinusoids with opaque medium. A preliminary report on forty-two cirrhotic patients studied in this manner has appeared elsewhere.[1] This paper is concerned with further observations in ninety-five cirrhotics (TABLE 1).

Case Material

The splenic portograms of 95 cirrhotics from our case material have been considered technically satisfactory for analysis of the intrahepatic vasculogram, the hepatogram, or both. Of the 95 cases, 84 had serial splenic portograms performed according to the technique described below and 11 had single-exposure splenic portograms (permitting evaluation of the vasculogram phase only). Of the 84 serial splenic portograms, 71 were performed in patients with intrahepatic portal venous obstruction only (cirrhosis), and 13 were performed in patients with cirrhosis complicated by extrahepatic obstruction (portal vein thrombosis partial or complete). Of the 71 cases of intrahepatic obstruction only 4 could not be used because of poor or absent vasculogram and hepatogram due to pathophysiology; in 3 there was failure of the medium to pass to the liver through the portal and splenic veins (proved later to be patent in all 3 cases) due, presumably, to a heavy runoff of opaque medium through large collaterals or an extensive network of small collaterals arising directly from the spleen or that part of the splenic vein immediately adjacent to it. In the fourth case, the medium reaching the liver was insufficient to produce either a diagnostic vasculogram or hepatogram, presumably because of heavy runoff of medium over collateral veins. In 2 other cases the study was terminated too soon to visualize the hepatogram phase, although the vasculogram phase was well visualized. These 2, therefore, have been added to the single-exposure group (TABLE 1).

Of the 13 cases with extrahepatic block, 7 had either complete obstruction of portal vein or sufficient obstruction to interfere seriously with visualization of the liver. In 5 cases the liver was sufficiently well visualized to permit study

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TABLE 1

DISTRIBUTION OF CIRRHOTIC CASES

Techniques and pathology	No. of cases
Cases available	
Serial technique:	
Intrahepatic obstruction	71
Intra- and extrahepatic obstruction	13
Single-film technique:	
Intrahepatic obstruction	11
Total	95
Cases used*	
Serial technique:	
Intrahepatic obstruction	65
Intra- and extrahepatic obstruction	5
Single-film technique:	
Intrahepatic obstruction	14
Total	84

* Because of pathophysiology, certain cases could not be used since vasculogram, hepatogram, or both were not adequate for interpretation.

of both phases in spite of the obstruction. In one case only the vasculogram phase could be evaluated (this, therefore, was added to the single-exposure group).

Of the 95 cirrhotics studied, the diagnosis has been established in 59 by biopsy and in 36 on clinical and laboratory grounds. In 33 cases with a clinical diagnosis, at least 2 positive liver function tests were obtained, and 2 or more of the following factors were present: (1) a positive history of chronic alcoholism, hepatitis, or other cause for liver damage, (2) hepatomegaly with or without splenomegaly, and (3) ascites. Eight liver-function tests were employed as routine: prothrombin, Hanger, thymol turbidity, alkaline phosphatase, A/G ratio, cholesterol and cholesterol esters, bromsulphalein, and serum bilirubin. In 3 cases only 1 laboratory test was positive, although the history and physical findings were sufficiently convincing to make this diagnosis the working clinical and discharge diagnosis of the patient. A number of the biopsy-proven cases showed either normal liver function or only 1 positive laboratory test.

It should be noted that various authors have made observations on both the vasculogram and hepatogram phases, but only minimal attention has been paid to this aspect of portal venography.[2-7] A notable exception is the work of Daniel *et al.*[8] who experimentally produced cirrhosis in rats and studied them by portal venography.

Technique of Splenic Portography

Details of the technique of splenic portography together with discussion of such aspects as complications encountered and preparation of the patient may be found elsewhere.[9-12] However, a brief description of the technique employed in this study is in order. Insertion of a No. 18 gauge spinal-type needle is made through the left lateral chest wall, usually at the level of the eighth or ninth interspace and in the axillary or posterior axillary line. An attempt is made to place the tip of the needle in the central portion of the spleen within 2 to 3 cm. of the hilum. Establishment of a satisfactory position of the needle tip is indicated by a free drip of blood from the hub of the needle and can also be verified by observing a test injection of 5 cc. of opaque medium under fluoroscopy to determine whether the opaque medium enters the splenic vein. Injection of 40 cc. of 70 per cent Urokon Sodium is then made for about 12 sec. (a range of 10 to 15 sec.). Serial films are made at 2, 4, 6, 8, and 12 sec. following the start of injection; exposures are then continued at 4-sec. intervals to 32 sec. and the final 3 exposures are at 37, 42, and 60 sec. Following the splenic injection, the extrahepatic vessels are filled first. Normally the opaque medium flows directly from the site of injection through the splenic vein and portal vein to the liver. In the presence of obstruction of the portal venous system various circuitous routes exist, carrying blood through collateral veins to the systemic circulation in a hepatofugal direction. Such obstructions are largely intrahepatic or extrahepatic; cirrhosis produces an intrahepatic type of obstruction. However, bland thrombosis of the portal vein, which occurs in 10 to 15 per cent of cirrhotics, produces extrahepatic obstruction in addition to intrahepatic obstruction in those cases so complicated. If extrahepatic obstruction is complete, visualization of the liver is frequently impossible, although even here bridging collaterals may, at times, span the obstructed vessel and carry opaque medium to the liver. In general, in the presence of obstruction, variable and as yet undeterminable amounts of blood are carried over the collateral veins and usually, except in certain complete extrahepatic obstructions, some blood passes at least to the sinusoidal level in liver.

The Normal Vasculogram

The normal intrahepatic portal vasculogram is best demonstrated, under the conditions of the technique employed, 2 to 12 sec. after injection is begun, but may be visualized somewhat longer (FIGURE 1). The right lobe branches are regularly opacified when the patient lies supine. The left lobe branches are frequently opacified only partially or not at all. This phenomenon is related chiefly to layering of the opaque medium, which has a greater specific gravity than that of blood.[9] This results in preferential filling of the right main intrahepatic branch, which is more posterior with the patient supine. A normal intrahepatic portal tree shows a symmetrical arborization with branches evenly distributed; branching vessels gradually diminish in size and there is a full compliment of small and fine end vessels.

The Abnormal Vasculogram

An abnormal vasculogram pattern is often encountered in cirrhosis. Some abnormality was noted in 86 per cent of this series (72 of 84 cases). Even when those cases with only slight deformity are excluded from the abnormal group, 65 per cent (55 of 84 cases) showed a very definite deformity in the vasculogram

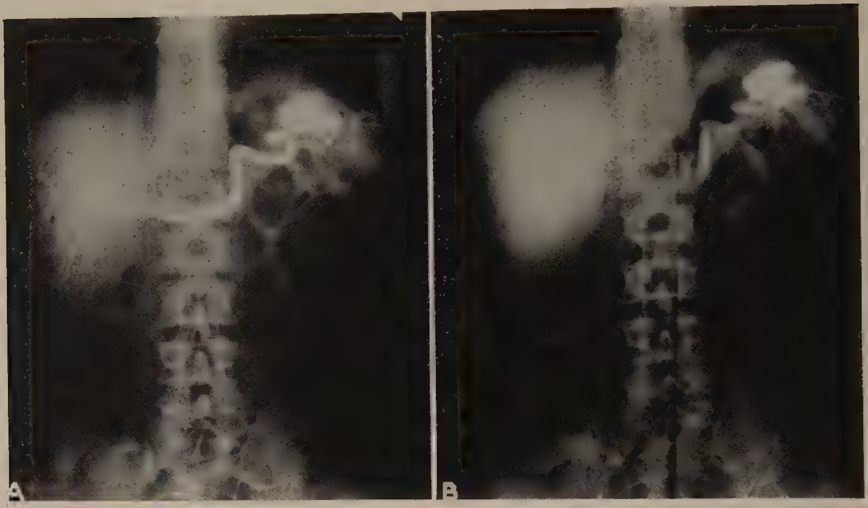

FIGURE 1. (*a*) Normal intrahepatic portal vasculogram. Note symmetrical distribution of vascular branches, normal tapering, and full complement of fine end vessels. Filling of right lobe branches is much more complete than that of the left. (*b*) Normal intrahepatic portal hepatogram. Note homogeneous opacification of liver, much more dense in right lobe than in left. Film *a* was obtained at 8 sec. after start of injection; film *b* at 20 sec.

(both serial- and single-exposure portograms included). The following variations in pattern have been observed in the cases of cirrhosis studied: (1) a normal pattern in a liver of normal size; (2) an over-all normal pattern, but with some elongation of vessels in an enlarged swollen liver; and (3) deformity of vasculature involving large vessels and small vessels in a normal-sized or contracted liver.

Large-vessel deformity consists of tortuosity of over-all pattern (gnarling), localized grouping of vessels, and irregularity of caliber of vessels. Small-vessel deformity consists of a paucity of smaller branches and irregularity of caliber. The deformity of the vascular pattern may be minimal, moderate, or severe (FIGURES 2 and 3).

An abnormal vasculogram also may be seen in other diseases. For example, spreading of branches with compression of vessels has been noted with space-occupying deposits such as primary and metastatic malignancy of liver. However, the vasculogram would appear to lend itself better to demonstration of the more diffuse changes of cirrhosis than the individual deposits of neoplastic disease, unless the latter are quite large.

The Normal Hepatogram

The hepatogram phase probably represents opacification of the sinusoids of the liver. This is in contrast to the mechanism involved with certain other methods of liver opacification; for example, in the pickup of thorium dioxide by the reticuloendothelial system of the liver. Since the opaque medium used with the technique described in this article passes through the vascular system

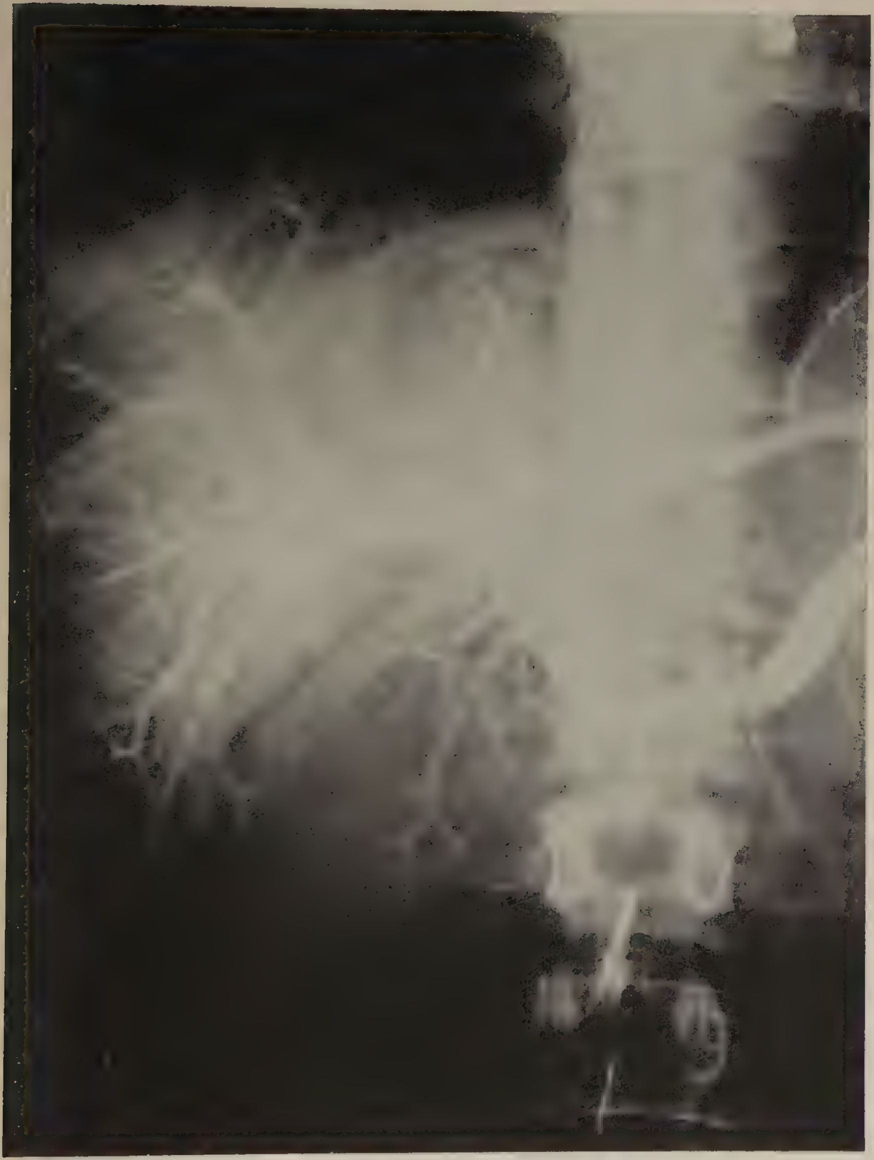

FIGURE 2. Liver biopsy cirrhosis. Film exposure was made at 12 sec. after start of injection. Vasculogram shows only slight abnormality; there is slight gnarling of major branches and slight irregularity of caliber of medium-sized branches.

of the liver and since opacification of sinusoids would be expected to produce a diffuse blush of density because of the multiplicity and generalized distribution of the sinusoids, it would appear that this is the most likely explanation of the hepatogram phase. This point, however, has not been proved experimentally.

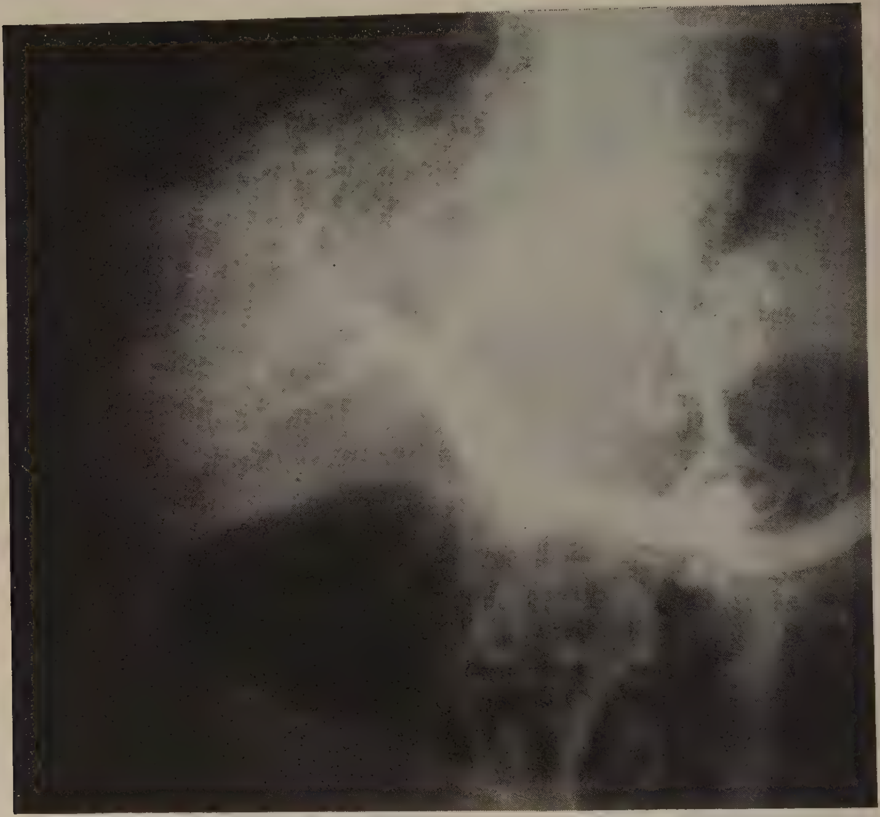

Figure 3. Marked vasculogram deformity in contracted liver of patient with cirrhosis. There is loss of symmetrical arborization of large and small vessels and marked irregularity of caliber of medium-sized vessels. Small liver is separated from lateral thoracic wall by ascites. Note coronary vein with large gastric and esophageal varices.

The Abnormal Hepatogram

The hepatogram phase takes place normally following or concomitant with the latter part of the vasculogram (figure 1). It begins usually 10 to 12 sec. after the injection is started and reaches a maximum at 16 to 24 sec. It may persist for as long as 60 sec., although it usually fades considerably by 37 to 42 sec.

In cases of cirrhosis the hepatogram may be either complete (opacification of the entire right lobe or both lobes occurring) or incomplete (in which regional or spotty opacification occurs). In either case the area opacified may be homogeneous or mottled. The more common type is that in which there is a radiolucent mottling against a homogeneously dense background (figures 4 and 5). Occasionally small or large scattered areas of opacification appear in a background of nonopacified liver. Technically adequate hepatograms were obtained in 69 of 84 cases (82 per cent) studied by the serial technique. The hepatogram was abnormal in 41 of 69 cases (59 per cent).

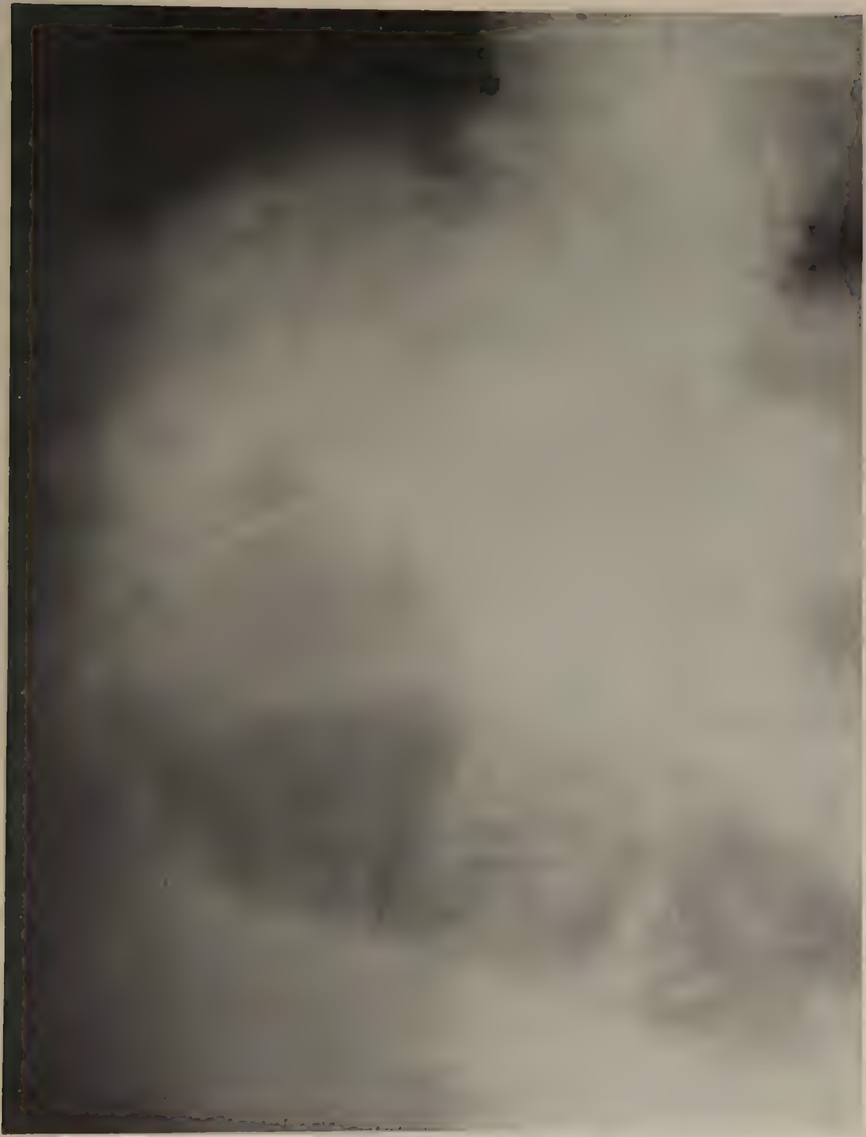

FIGURE 4. Hepatogram phase of case shown in FIGURE 3. Some opaque medium remains in intrahepatic portal branches. Hepatogram shows mottled pattern. Nodular border of liver can be distinguished by virtue of sinusoidal opacification. Note that two phases of vasculogram and hepatogram may exist simultaneously.

Neoplasm of the liver is particularly well demonstrated by the hepatogram phase,[1, 3-4, 7, 13] and radiolucent defects of varying size may be found throughout the opacified liver. This better definition of neoplasm than of cirrhosis is probably related to a relatively normal blood supply as well as to the presence

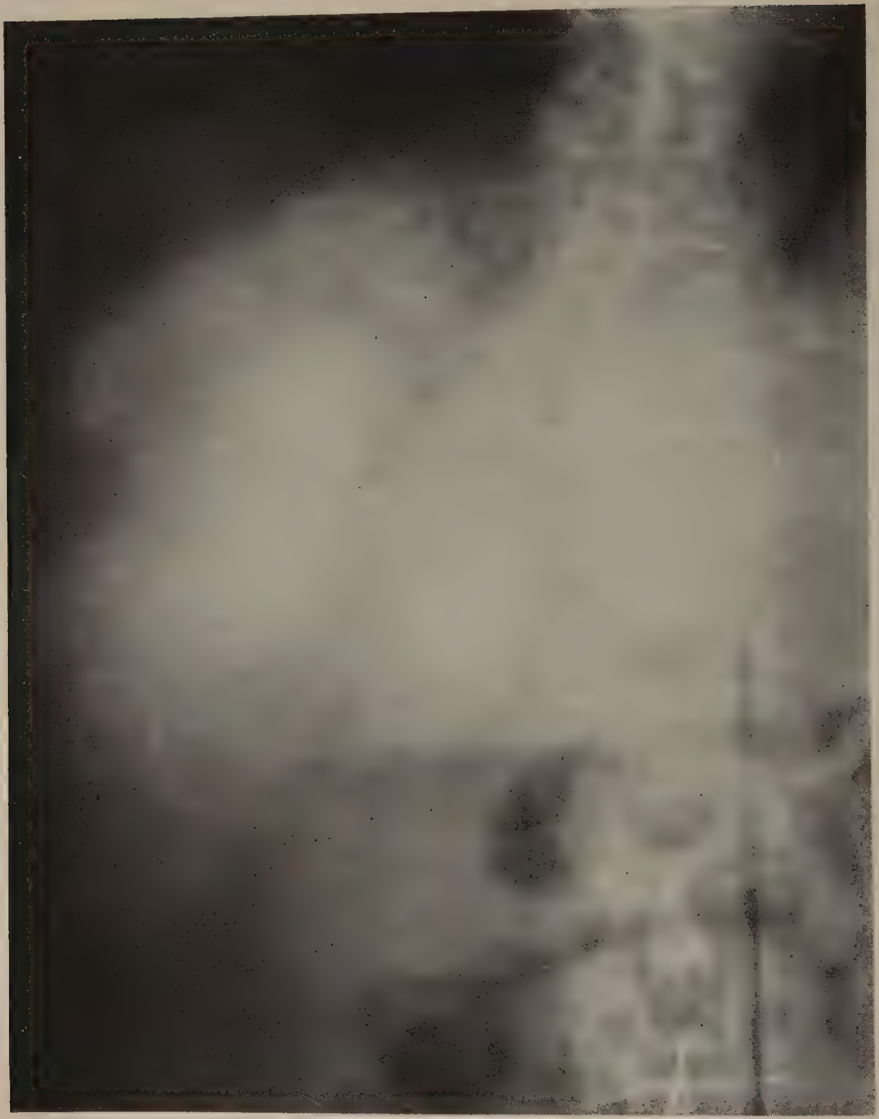

FIGURE 5. Hepatogram phase in patient with cirrhosis. Density of opacification, probably related to amount of medium delivered to a particular area during vasculogram phase, varies considerably in various parts of liver. There is also some radiolucent mottling even within densely opacified areas, the explanation of which is not known. See text for discussion.

of normal liver substance in those portions not invaded by tumor. In cirrhosis a more diffuse process involving the entire parenchyma is present so that any opacification that occurs takes place in an abnormal parenchyma where blood supply has been altered. Therefore the irregular radiolucent defects (that is, mottling) are apt to be more irregular and less well defined (FIGURES 4 and 5).

In general, the hepatogram tends to show the distribution displayed by the vasculogram. However, at times there may be no strict correlation between the vasculogram and the hepatogram phases. Thus, livers with a fairly uniform portal blood supply demonstrated in the vasculogram may not always show a hepatogram throughout the same area. Broadly speaking, however, the degree of vascularity and vascular patency of an area would appear significantly to influence production of the hepatogram phase in that area.

It is quite possible that blood-flow mechanisms[14] known to exist in the normal liver may play some role in the production of the abnormal hepatogram patterns that are encountered. Intrahepatic venovenous shunts,[3, 15] portal to hepatic and, also, arteriovenous shunts have been described in the liver. A mechanism that might permit bypassing of sinusoids (for example, portal to hepatic shunts) or would permit dilution by nonopacified blood (for example, arteriovenous shunts) would be expected to result in a relatively less dense hepatogram in those areas so affected. Localized areas of radiolucency as well as generalized diminished density might be explained in this manner. A further contributing factor to the abnormal hepatogram pattern may be a choked-off blood supply due to the fibrosis of cirrhosis.

In addition to demonstrating the changes within the liver itself, the liver contour may be delineated so that a nodular liver may be quite well outlined by the hepatogram phase.

Relationship of Vasculogram to Hepatogram

The relationship of the normality and abnormality of the vasculogram to the hepatogram was evaluated in sixty-nine cases of cirrhosis (TABLE 2). The most frequent pattern was the occurrence of an abnormal hepatogram following an abnormal vasculogram; also, a normal hepatogram frequently occurs with an abnormal vasculogram. The other two possible combinations occur less frequently, namely a normal vasculogram with a normal hepatogram and a normal vasculogram with an abnormal hepatogram.

It has been reported that no relationship has been observed between routine liver-function tests and the normality or abnormality of the vasculogram in cirrhosis.[1] However, an abnormal vasculogram can be used as a sign of cirrhosis even when liver function tests are normal. An abnormal vasculogram was shown by eleven of thirteen biopsied cirrhotics in this study who had essentially normal response in liver-function tests (that is, at the time of examination their livers were in a compensated state and showed abnormal response to one function test at most). It is noteworthy that an abnormal vasculogram pattern is not pathognomonic of cirrhosis since it may be seen in other situations, for example, with cavernomatous transformation of the portal vein.[1]

TABLE 2
INCIDENCE OF FOUR COMBINATIONS OF VASCULOGRAMS AND HEPATOGRAMS*

	Normal vasculogram	Abnormal vasculogram
Normal hepatogram	7	21
Abnormal hepatogram	5	36

* Total number of cases evaluated: 69.

Conclusions

Satisfactory opacification of the liver in two phases can be obtained with the serial technique following percutaneous splenic injection when there is a satisfactory delivery of opaque medium to the liver. This took place in 69 of 84 cases (82 per cent) considered technically satisfactory.

An abnormal vasculogram has been found in 65 to 85 per cent of cirrhotics studied (serial and single exposures considered together).

An abnormal hepatogram occurred in 41 of 69 cases of cirrhosis (59 per cent), using serial splenic portograms only.

In general, the vasculogram phase is more useful in the diagnosis of cirrhosis than the hepatogram phase.

Four different combinations of vasculogram and hepatogram are possible; the occurrence of abnormal vasculogram with abnormal hepatogram and abnormal vasculogram with normal hepatogram are the most common combinations.

The technique described may also afford information in other disease processes.

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PANCREATOGRAPHY*

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The new technique of pancreatography[1, 2] has increased our knowledge of the pathological process in pancreatitis and has helped to establish principles of treatment based on anatomic and physiological observations. It has been proved to be of help also in the treatment of pancreatic tumors and of trauma.

When the sphincter of Oddi is sectioned transduodenally, a fine plastic tube can be inserted for a distance of 4 to 5 cm. into the pancreatic duct opening found in the posterior wall of the ampulla of Vater. Radiopaque solution (70 per cent sodium acetrizoate, or Urokon sodium) is injected slowly, about 5 cc. during a 5-min. period, the last 2 cc. being introduced during the X-ray exposure. The excess will flow into the duodenum, around a tube, or through the accessory pancreatic duct when it is present. If the pancreatic duct is dilated, or if the pancreas has been incised to remove stones, the plastic tube is left *in situ* for drainage.[3] Two sutures are placed to hold this tube in the pancreatic duct, and it is then led up the common duct and out through the cystic duct, or alongside a T-tube in the common duct. Postoperative serial pancreatographic studies can be carried out to follow the regression of inflammation or of cysts (FIGURE 1).

Pancreatographic studies were found to be of value for the following indications:

Study of the normal anatomy of the human pancreatic duct system and its aberrations, and determination of the presence of acute inflammation or edema. As a rule, when acute inflammation is present, the pancreas is swollen and hard; occasionally it is surrounded by an exudate or by areas of fat necrosis. However, it may be buried retroperitoneally, and the only evidence of an acute process may be increased firmness and prominence of the lobules or a sensation of bogginess. In the absence of acute inflammation, the pancreatogram reveals only the main ducts (FIGURES 2, 3, and 4). With mild residual edema, the smaller ducts are visualized as a result of a decrease in the pressure of pancreatic secretion. In the presence of acute inflammation the duct epithelium loses its characteristic quality of semipermeability, and the radiopaque solution permeates the acinar tissue.[4] The acute process may be localized, as in the body or tail, or may involve the whole pancreas. Serial pancreatograms may be made after the resolution of acute inflammation. When the acute process subsides, the tissues are no longer opacified (FIGURES 5, 6, and 7). It was noted that pancreatic juice flowing from an acutely inflamed organ contained active trypsin instead of trypsinogen[5] (FIGURE 8). This observation was applied as a delicate test to determine the toxicity of various radiopaque solutions (FIGURE 9 and TABLE 1).

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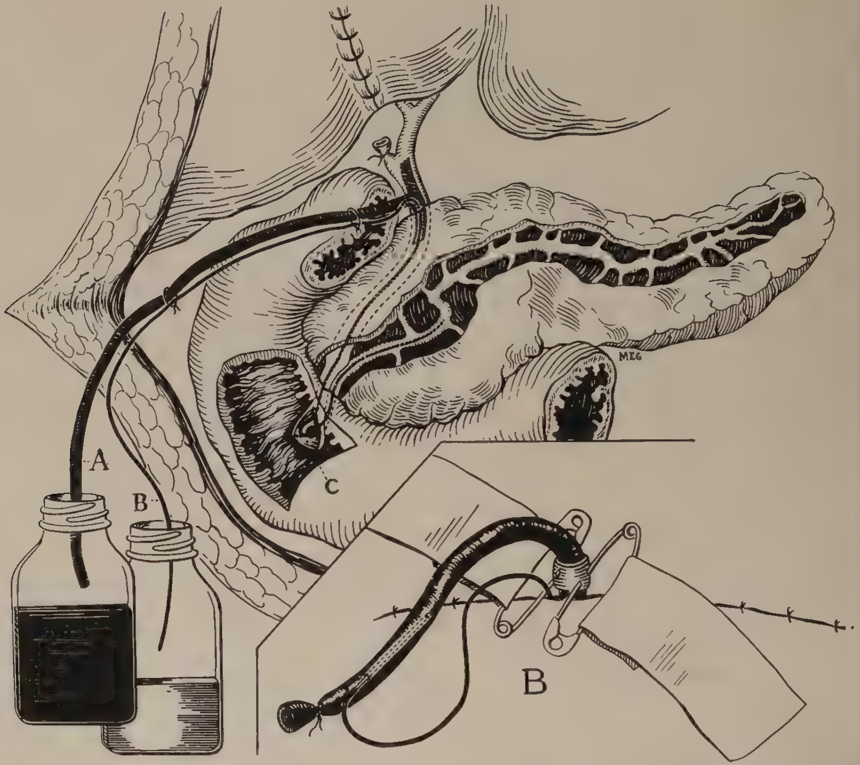


FIGURE 1. Intubation of the pancreatic duct. After section of the sphincter of Oddi (*C*), the end of a plastic tube was placed up the pancreatic duct, and the other end (*B*) brought out through the duodenum, up the common bile duct, and alongside a T-tube (*A*) or through the cystic duct.

Demonstration of the presence of dilatation of ducts. In advanced chronic pancreatitis the ducts are typically dilated and often sacculated. If the dilatation is marked, the duct can be drained advantageously for several weeks through an indwelling plastic tube.

Demonstration of the presence of cysts, cystic dilatations, and pseudocysts. True cysts of the head of the pancreas cannot be palpated if they are acute and small; pancreatographic studies will demonstrate them.[6] Reduction of the pressure in the pancreatic duct by means of sphincterotomy and drainage of the duct will cause shrinkage and eventual disappearance of the cyst (FIGURE 10) Similarly, the cystic dilatations and abscesses that occur in the tail of the pancreas as a result of recurrent attacks will diminish in size and heal after sphincterotomy (FIGURE 11).

The same principle can be applied to pseudocysts of the pancreas, which form essentially as a result of the rupture of fine ducts into the retroperitoneal space during an acute necrotizing process. These pseudocysts enlarge and persist because of the increased pressure in the pancreatic ducts resulting from spasm

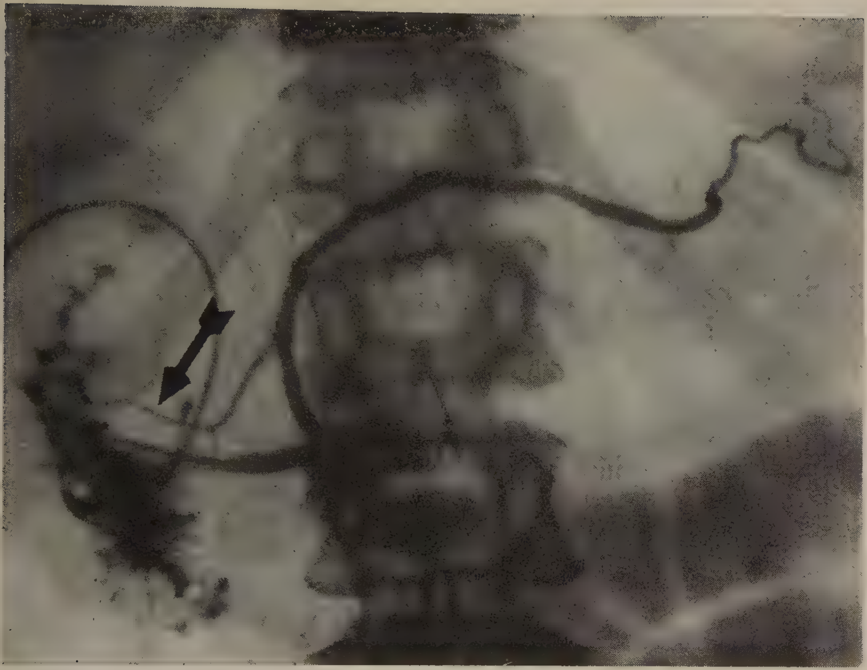


Figure 2. Operative pancreatogram. Injection through the plastic tube reveals a normal pancreatic duct system. Note accessory duct (arrow).

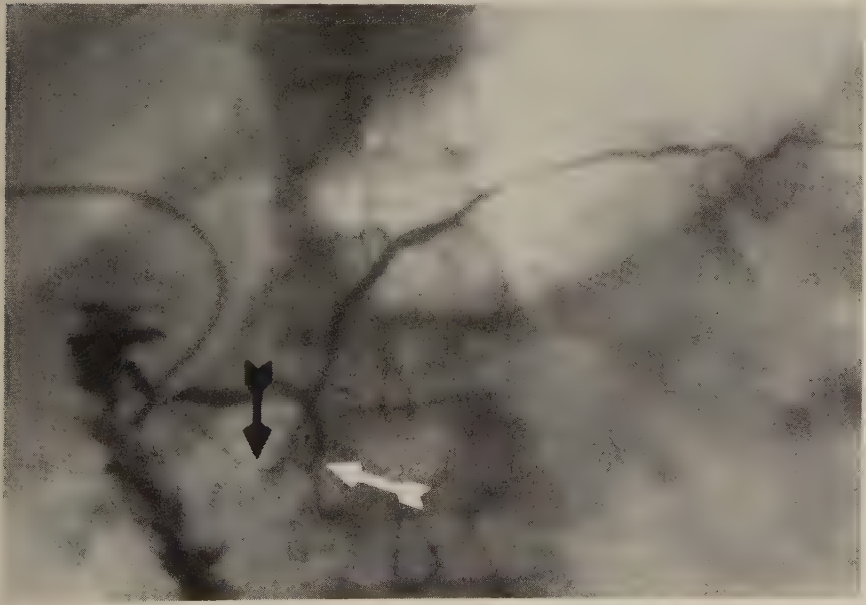


Figure 3. Pancreatogram showing unusual anatomy. The duct of Wirsung makes a complete loop (white arrow) while the accessory duct of Santorini (black arrow) originates at the base of the loop.

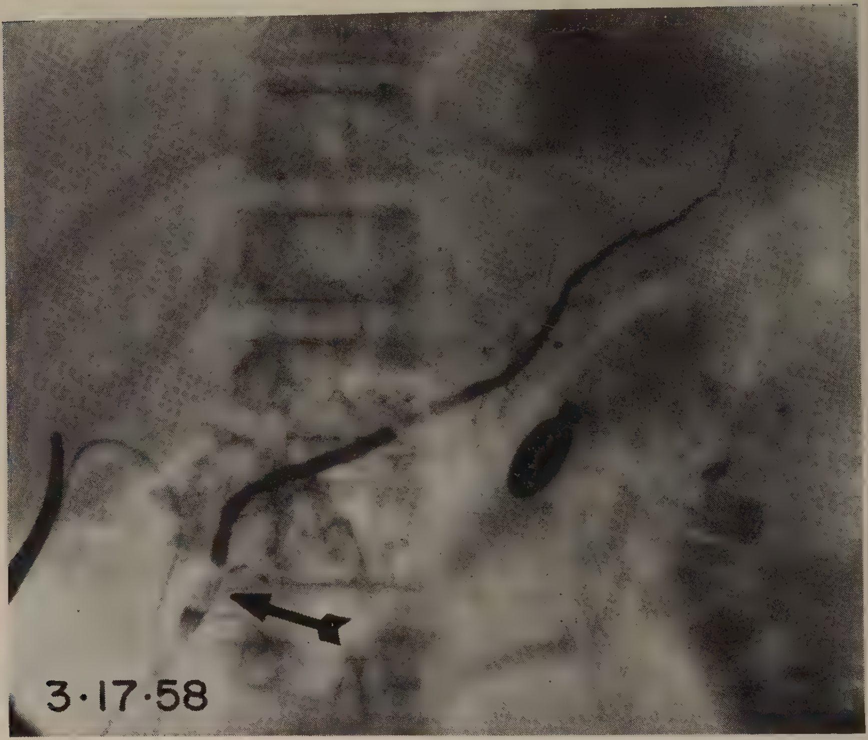


FIGURE 4. Absence of accessory duct. This study, performed through a plastic tube held in place by a tiny balloon inserted into the duct of Wirsung (arrow), shows no communication with the accessory duct of Santorini.

of the sphincter of Oddi. Since the pseudocysts are in direct communication with the main pancreatic ducts, pancreatography will fill them and demonstrate their presence and extent. When a tube is left in place, in either the pancreatic duct or the pseudocyst, the disappearance of the pseudocyst can be followed by serial pancreatograms (FIGURE 12). Similarly, a persistent pancreatic fistula resulting from either marsupialization of a pseudocyst or accidental trauma will close readily if the intraductal pressure is reduced by sphincterotomy.

Search for a cyst in the presence of persistent high amylase level. It has been our experience that, if a patient has a persistently high serum amylase level after recovery from an acute attack of pancreatitis, the presence of a pseudocyst should be suspected. At times, even with the abdomen open, such a pseudocyst cannot be palpated because of the presence of massive inflammatory adhesions matting the transverse colon and stomach over the pancreatic area. A pancreatogram will reveal the position and extent of such a pseudocyst (FIGURE 13). On one occasion the pseudocyst was found to lie in the posterior mediastinum (FIGURE 14).

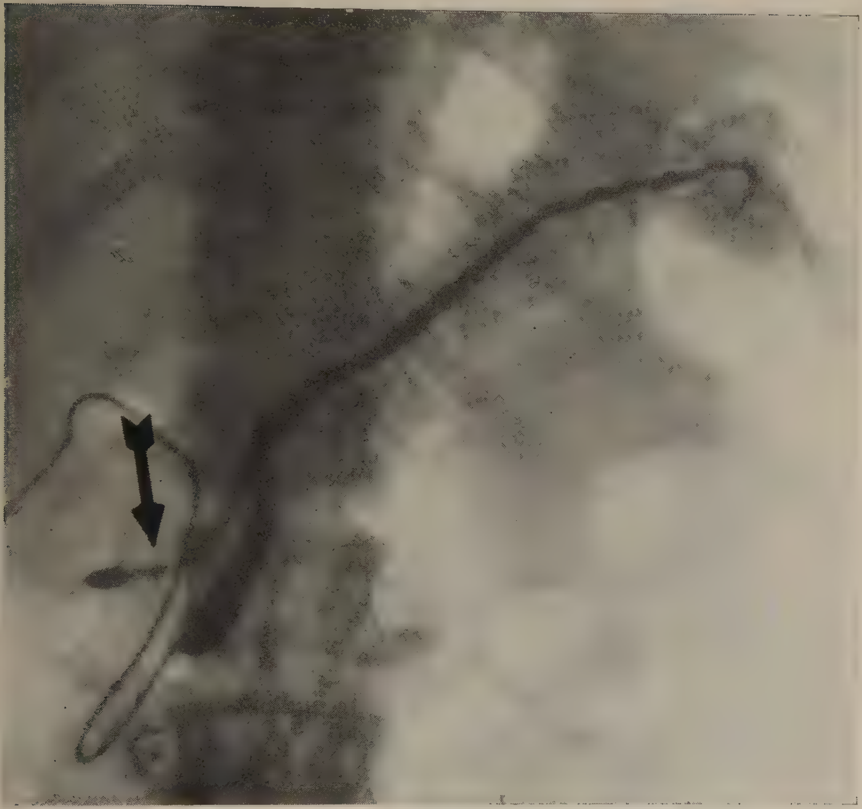


FIGURE 5. Faint opacification of the pancreas in a case of pancreatitis in which the inflammation has almost entirely subsided. Note opacification of the finer pancreatic ducts. The duct of Wirsung and the accessory duct of Santorini (arrow) are markedly dilated.

Demonstration of patency or obstruction of main pancreatic duct. Since the objective of sphincterotomy, in addition to avoidance of further incidents of biliary reflux, is to reduce the pancreatic intraductal pressure, an essential corollary is that no other obstructive factor be present in the duct. Such an assurance can be obtained only by an operative pancreatogram. If partial obstruction is produced by stone or stricture, the stones should be removed by direct incision of the pancreas (FIGURE 15) or the pancreas resected distal to a stricture (FIGURE 16). If multiple stones are in the duct of Wirsung, which traverses the head of the pancreas and cannot be removed, the pancreas should be transected in the body and a loop of jejunum interposed—a "split" pancreaticojejunostomy (FIGURE 17). If the tail of the pancreas has been completely destroyed by necrosis, a caudal pancreaticojejunostomy should be done (FIGURE 18). Similarly, successful treatment of a pseudocyst or pancreatic fistula cannot be achieved by sphincterotomy alone in the presence of partial

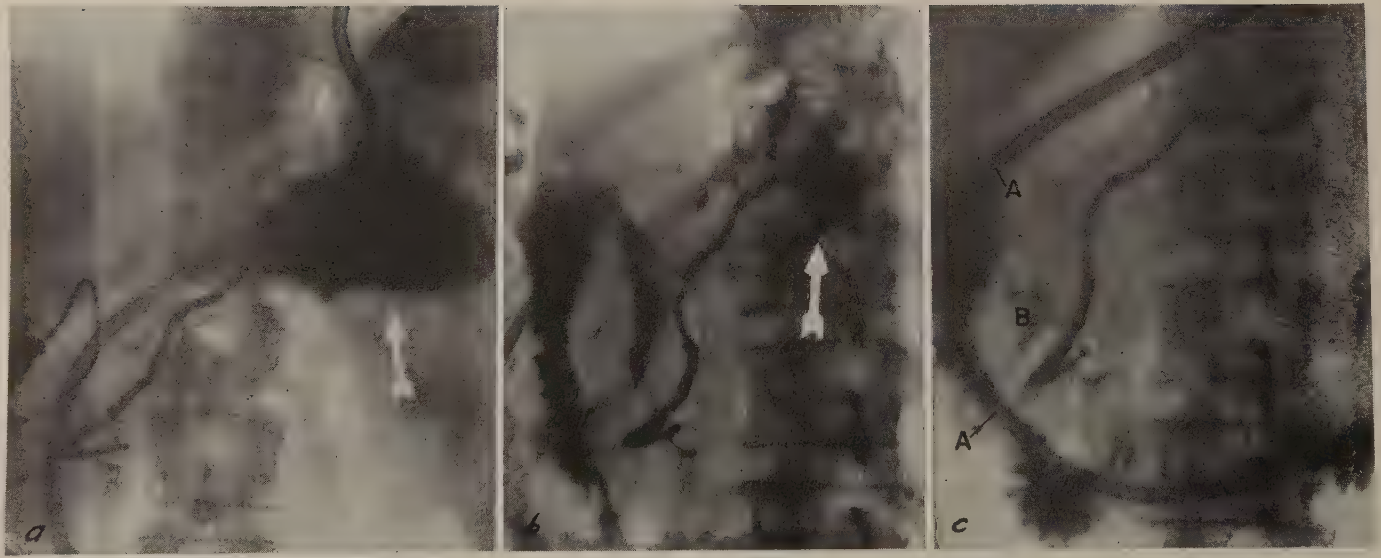


FIGURE 6. Disappearance of opacification with resolution of acute inflammation. Operative pancreatogram (*a*) shows opacification of the tail of the pancreas, site of an acute inflammatory process. At this time, pancreatic juice contained more than 50 per cent active trypsin. A study 2 weeks later (*b*) showed marked shrinkage of the area of opacification. Two weeks later (*c*) the area of opacification was completely gone. At this time the pancreatic juice contained no active trypsin. Note in *c* a Rehfuss tube (*A*) lying in the duodenum, and the accessory duct of Santorini (*B*).

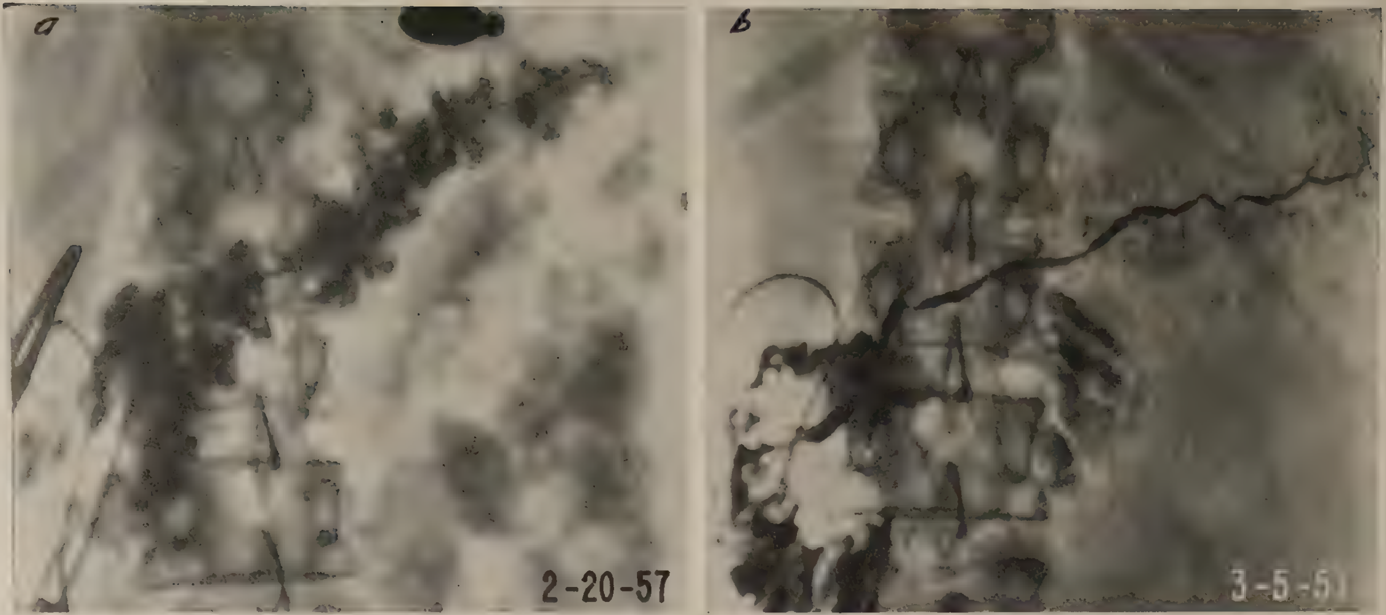


Figure 7. Disappearance of opacification of the whole pancreas. (*a*) Operative pancreatogram, while the pancreas was still swollen and edematous, has all the acinar tissue opacified. Two weeks later (*b*) the acute process was almost completely resolved, with only a few fine ducts visualized in the tail of the pancreas.

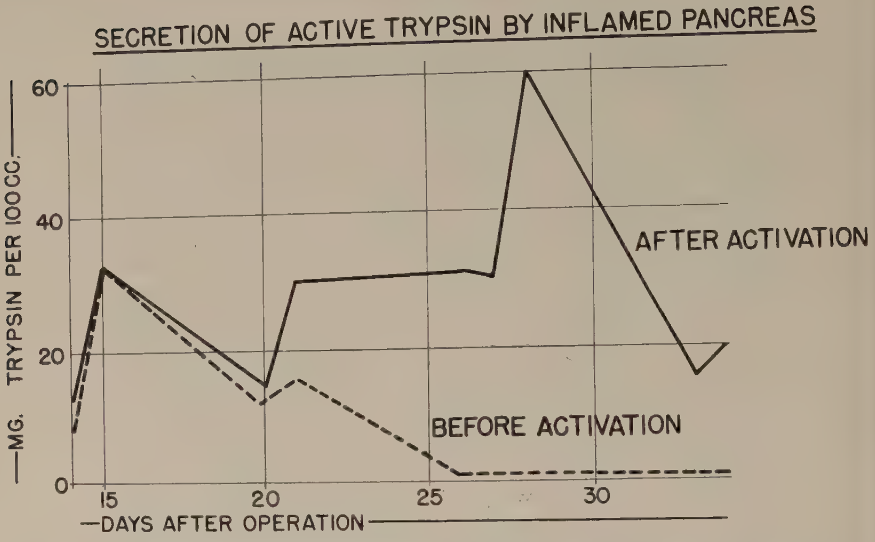


FIGURE 8. Correlation of acute inflammation with the presence of active trypsin in the pancreatic juice. Analysis of the pancreatic juice in the case illustrated in FIGURE 6 showed almost total activation of trypsinogen during the first 3 weeks after operation. Following this, opacification disappeared and the active trypsin ceased to be present in the pancreatic juice.

obstruction of the main pancreatic duct. Obstruction of a pancreatic duct by early carcinoma also can be demonstrated (FIGURE 19).

Demonstration of complete absence of connection between main pancreatic duct and cyst. Old chronic cysts of the head of the pancreas often lose all connection with the main pancreatic duct. Although sphincterotomy is essential to prevent further progress of the basic disease of pancreatitis, the cyst itself must be anastomosed to the jejunum to obliterate it. Similarly, mesenteric cysts, which are residual collections of the exudate that extended into the mesocolon during a previous acute attack, can be excised if they are thin-walled, or drained if they are old and thick-walled (FIGURE 20).

Demonstration of obstruction of pancreatic duct by utilizing accessory pancreatic duct. At times, the lower end of the pancreatic duct is obstructed or destroyed by a severe inflammatory process. It then becomes difficult to locate the opening of the pancreatic duct into the posterior wall of the ampulla of Vater, because there is no flow of pancreatic juice. Under such conditions the accessory pancreatic duct can be intubated, and the duct system, as well as the site of obstruction, visualized (FIGURE 21).

Deliberate opacification of the whole pancreas. The principles illustrated by these observations may be applied to delineate the presence of a tumor such as an adenoma. Although a suitable case in which an adenoma is visualized has not been available, we have been able to visualize the whole pancreas at will and, on occasion, to demonstrate the absence of an extra-acinar mass. Iodopy-

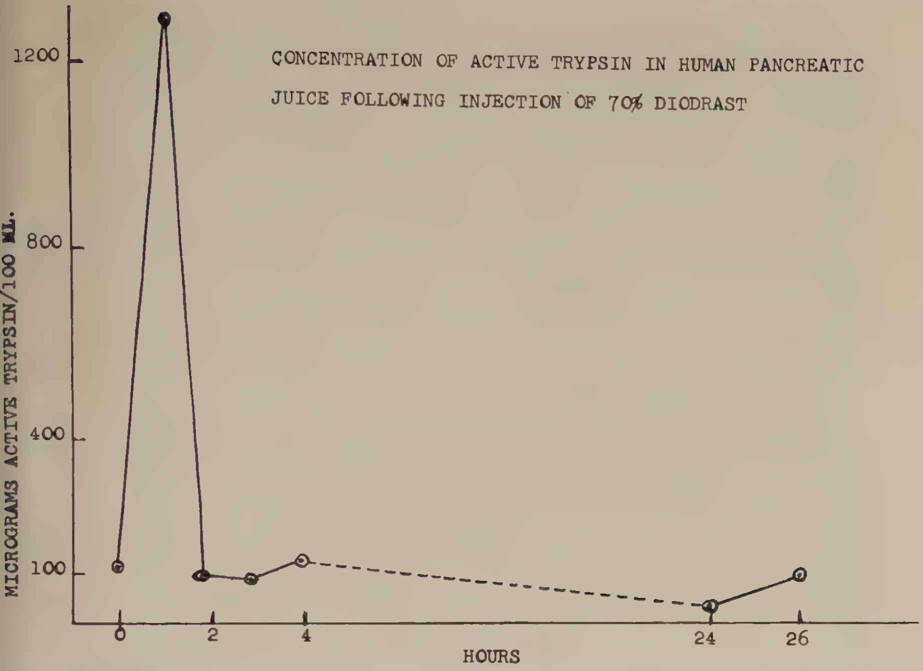


FIGURE 9. Test for the irritative action of radiopaque solution. The injection of 70 per cent Diodrast produced transient increase of active trypsin in the pancreatic juice. Note the rise of active trypsin from 100 to 1200 mg. per cent within 1 hour after the injection of this solution.

TABLE 1
REACTION OF PANCREAS TO VARIOUS RADIOPAQUE SOLUTIONS

Patient	Radiopaque solution (percentages)	Active trypsin (µg./100 cc.) Control	Active trypsin (µg./100 cc.) Postinjection
J	70 Urokon	74	77
J	70 Diodrast	34	82
J	50 Neo-Iopax	34	55
D	70 Diodrast	0	969
C	70 Urokon	98	77
C	70 Diodrast	103	255

racet (Diodrast) produces a transient acute inflammation of the duct epithelium. If the normal pancreas is injected to visualize the duct system and then reinjected after 10 min., all the acinar tissue will be opacified, and any structure not in continuity with the duct system should be visualized (FIGURE 22).

Demonstration of rupture of pancreas following trauma. When the pancreas is involved in trauma, rupture of its ducts is often difficult to identify, especially if the injury occurs retroperitoneally. The principle of treatment of an injured

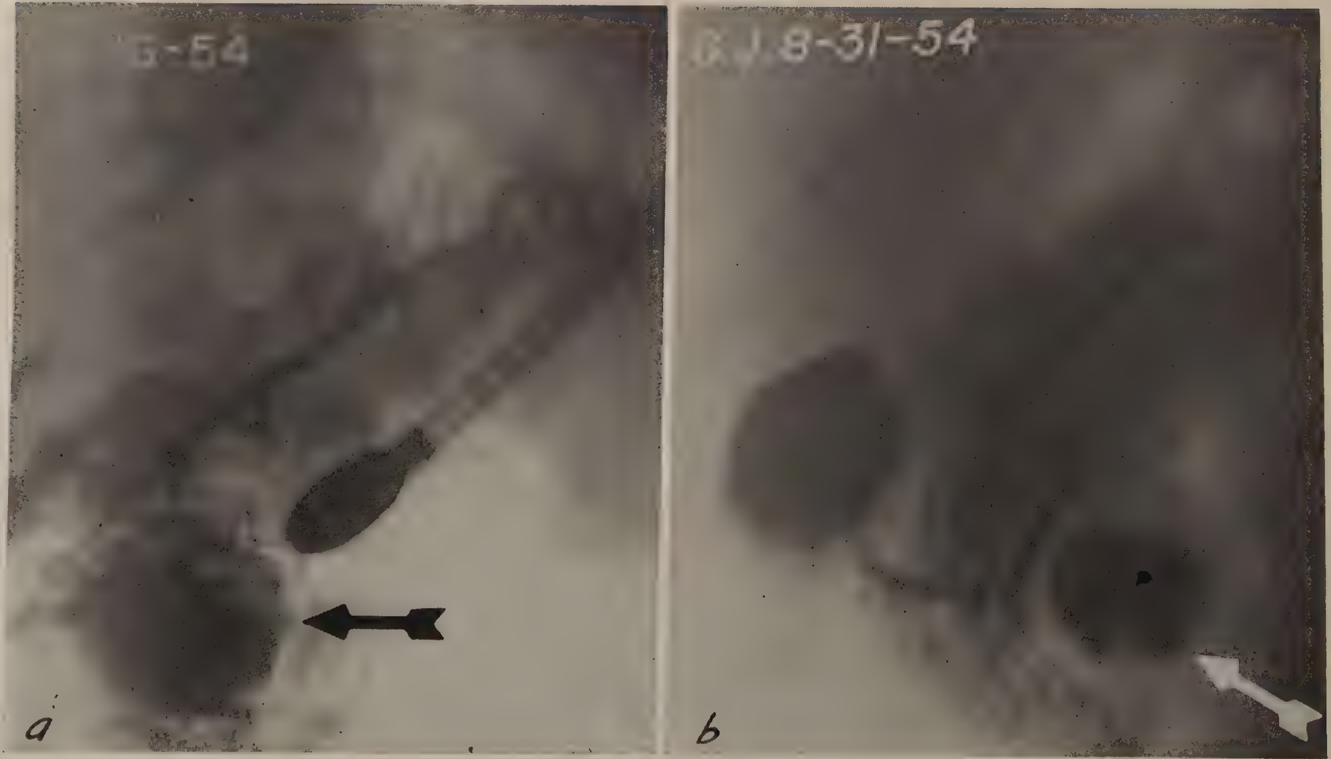


FIGURE 10. Visualization of acute cyst in the head of the pancreas. (*a*) Operative pancreatogram revealed small acute cyst in head of the pancreas (arrow). Two weeks later (*b*) pancreatographic study revealed marked diminution in size of cyst (arrow).

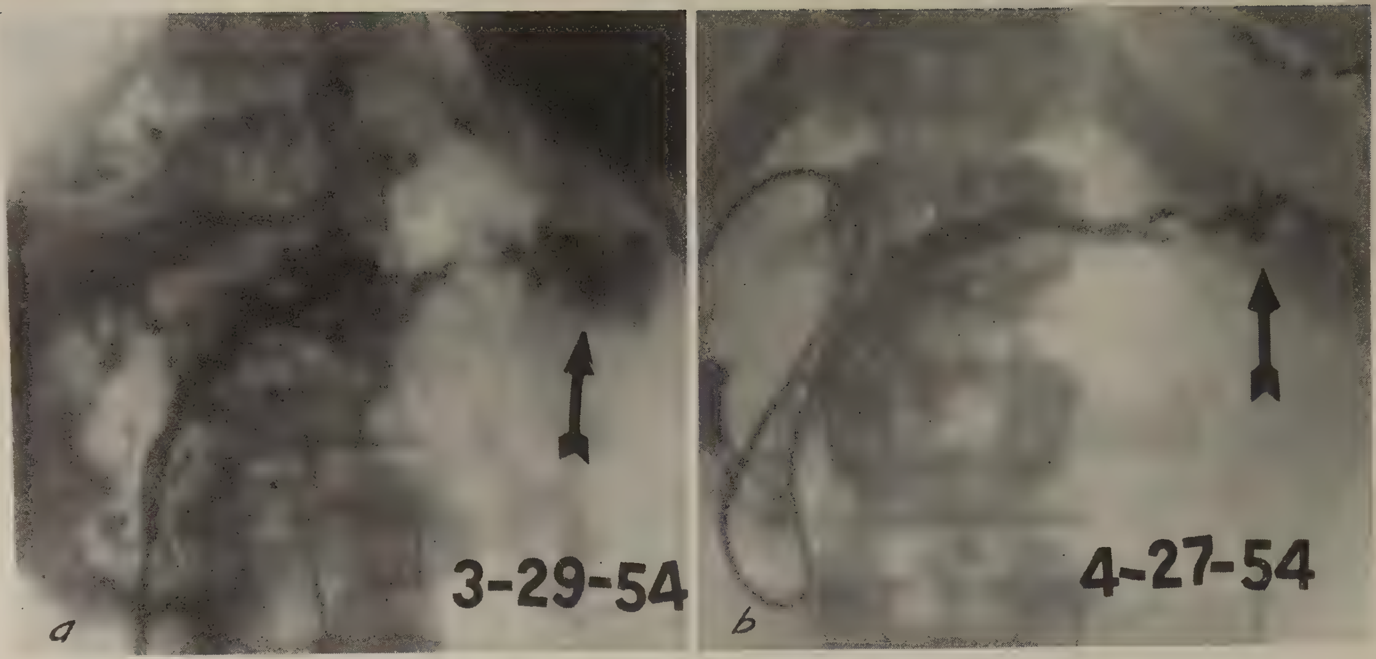


FIGURE 11. Cystic dilatation of the tail of the pancreas. Operative pancreatogram (*a*) revealed marked cystic dilatation of tail (arrow). Four weeks later (*b*) cystic dilatations in the tail (arrow) showed marked diminution.

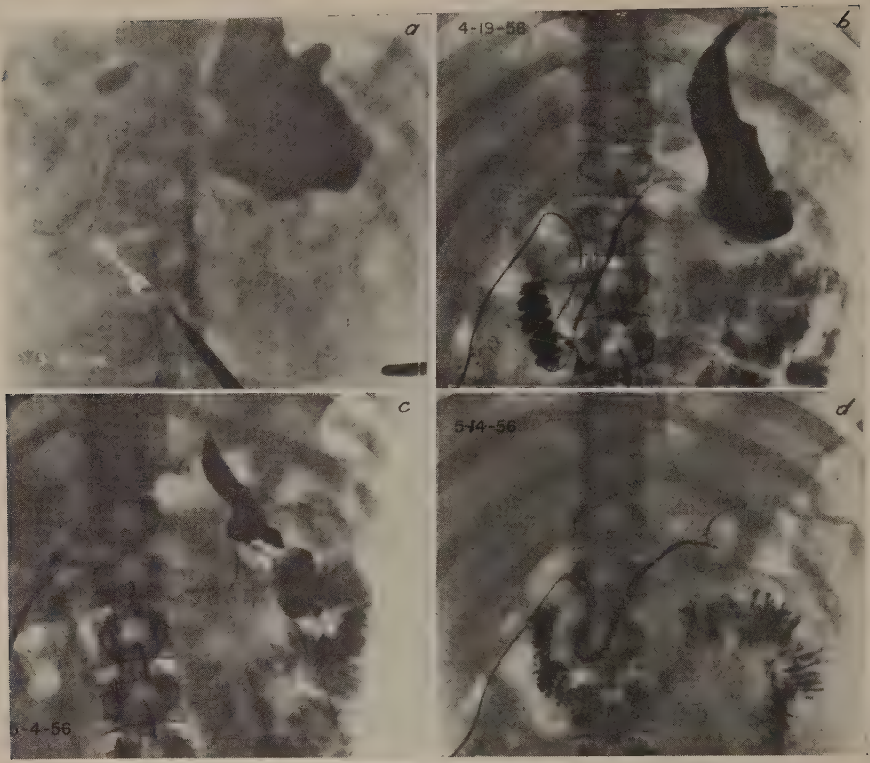


FIGURE 12. Resolution of a pseudocyst following sphincterotomy. (*a*) Operative pancreatogram through a tube lying in the duct of Wirsung (arrow) delineated a huge pseudocyst. A study (*b*) made 24 days later showed the pseudocyst to be about one-fourth its original size. Two weeks later (*c*) the pseudocyst was much smaller, and 10 days later (*d*) it was completely gone.

pancreatic duct is reduction of the intraductal pressure and drainage of the duct. This can be achieved by section of the sphincter of Oddi and drainage through a plastic tube left *in situ* and brought out through the cystic duct. An operative pancreatogram will detect the point of rupture. The healing of the duct can be followed by serial pancreatograms.

Comment

The procedure of pancreatography is no more difficult than the performance of operative cholangiography and is without danger if adequate precautions are taken. It requires, however, a prior transduodenal sphincterotomy and intubation of the pancreatic duct. Since manipulation of the pancreas is involved, as well as the injection of an irritating solution that can produce a transient pancreatitis, certain precautions are essential. Sphincterotomy is contra-

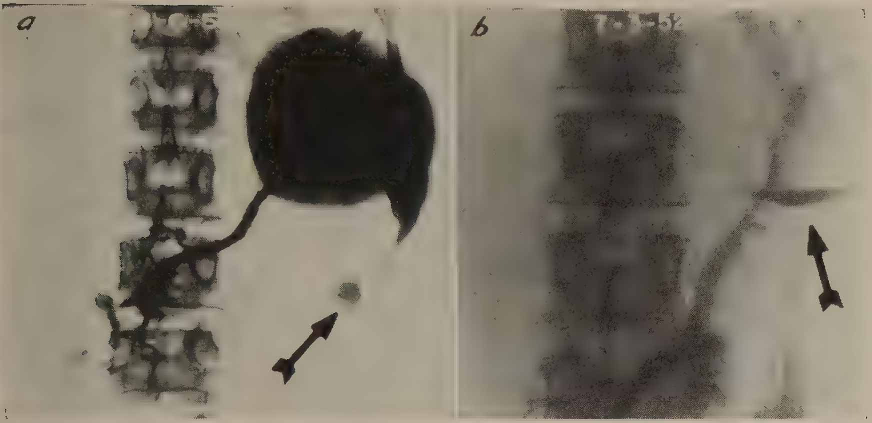


FIGURE 13. Demonstration of the presence of an unsuspected pseudocyst. An operative pancreatogram (*a*) revealed the presence of a huge pseudocyst lying in the left upper quadrant behind an inflammatory mass consisting of stomach, transverse colon, and spleen. This pseudocyst extended down to the sigmoid mesocolon (arrow). One month later pancreatographic study (*b*) revealed only a small residual space (arrow).

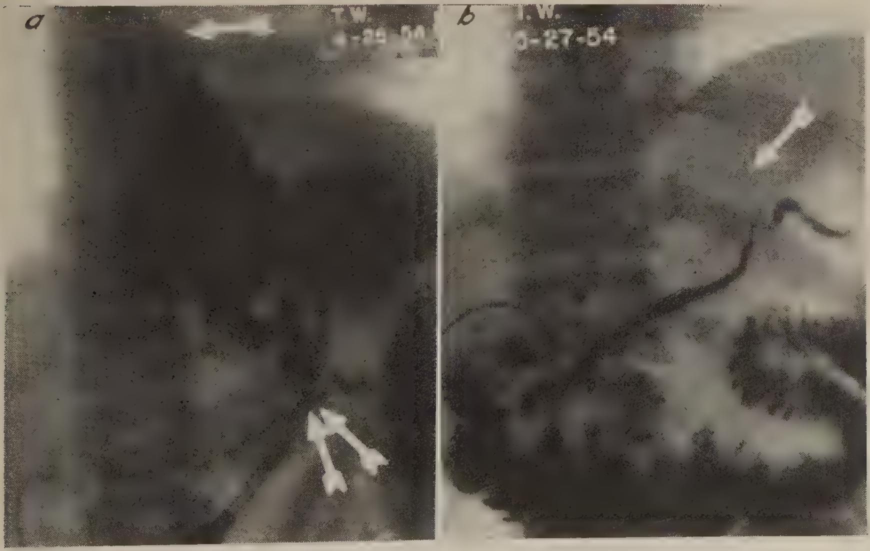


FIGURE 14. Demonstration of an unsuspected pseudocyst in the posterior mediastinum. An operative pancreatogram (*a*) following section of the sphincter of Oddi showed a break in the pancreatic duct near the tail (two arrows), with an extension upward into the posterior mediastinum as far as the sixth thoracic vertebra (one arrow). One month later (*b*) this enormous pseudocyst completely disappeared, with only a small space (arrow) remaining at the site of the previous tract.

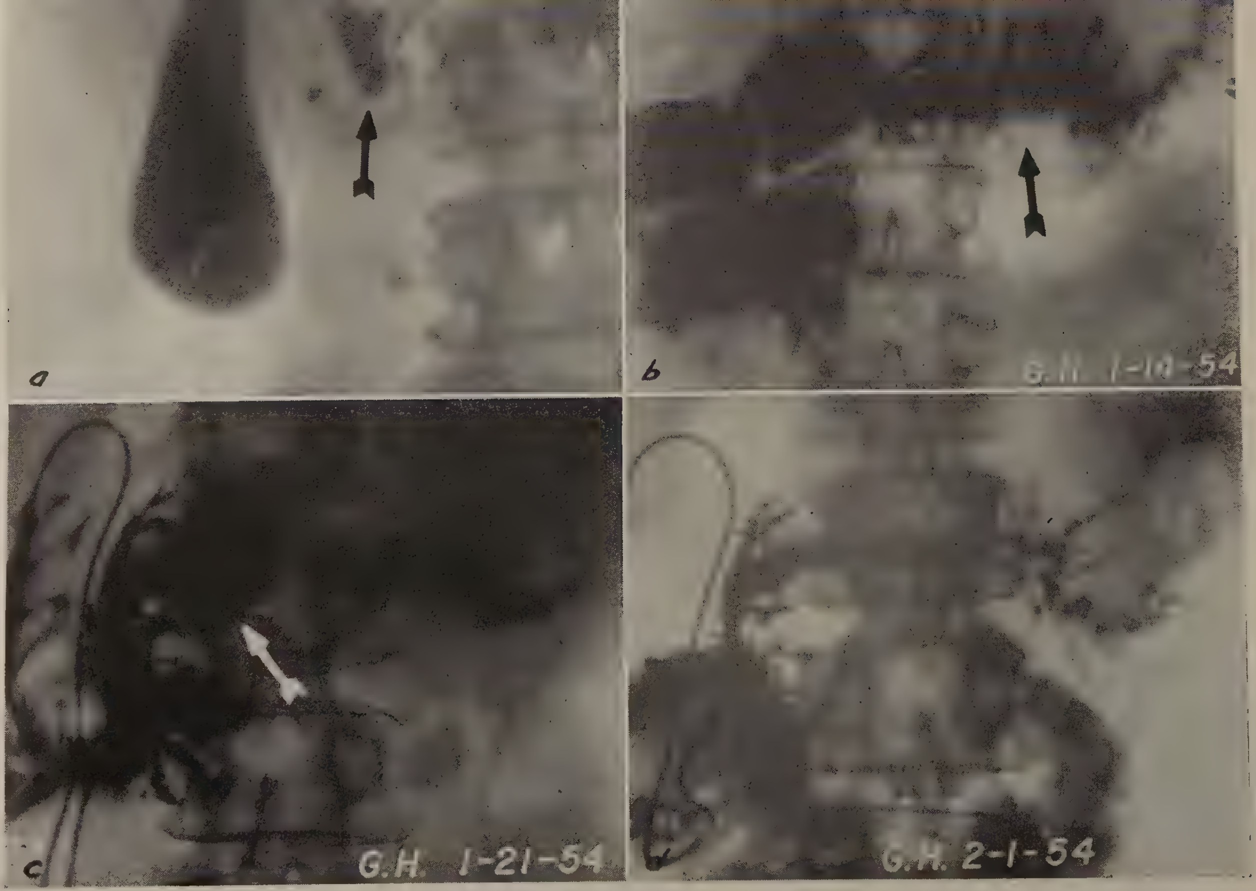


Figure 15. Demonstration of partial obstruction of pancreatic duct by a calculus. Calcification (arrow) in the head of the pancreas (*a*) was found by operative pancreatography (*b*) to be a markedly irregular calculus lying in a cyst in the head of the pancreas, partially obstructing an enormously distended duct behind it (arrow). The calculus was removed by an incision in the head of the

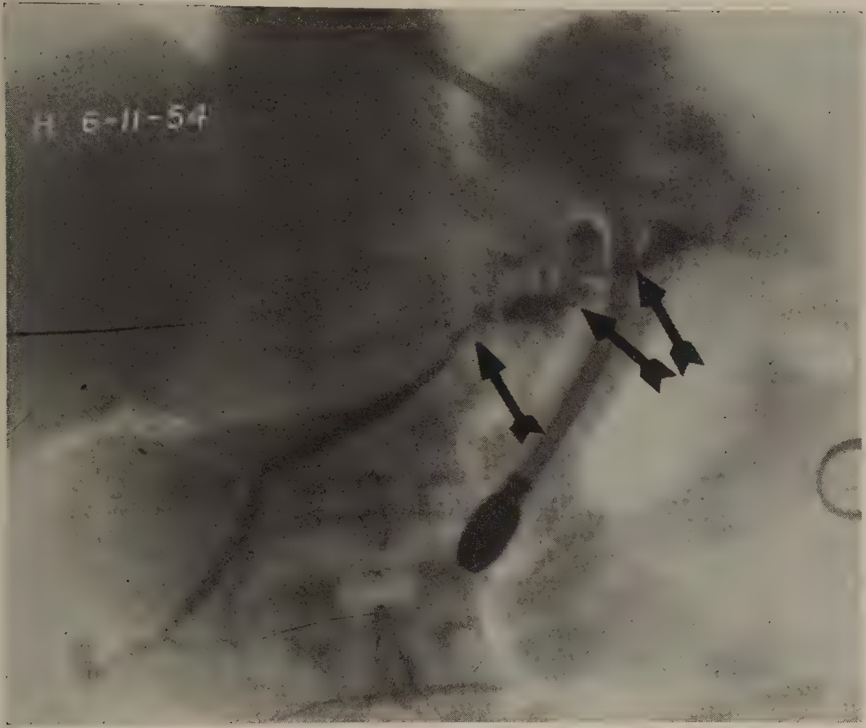
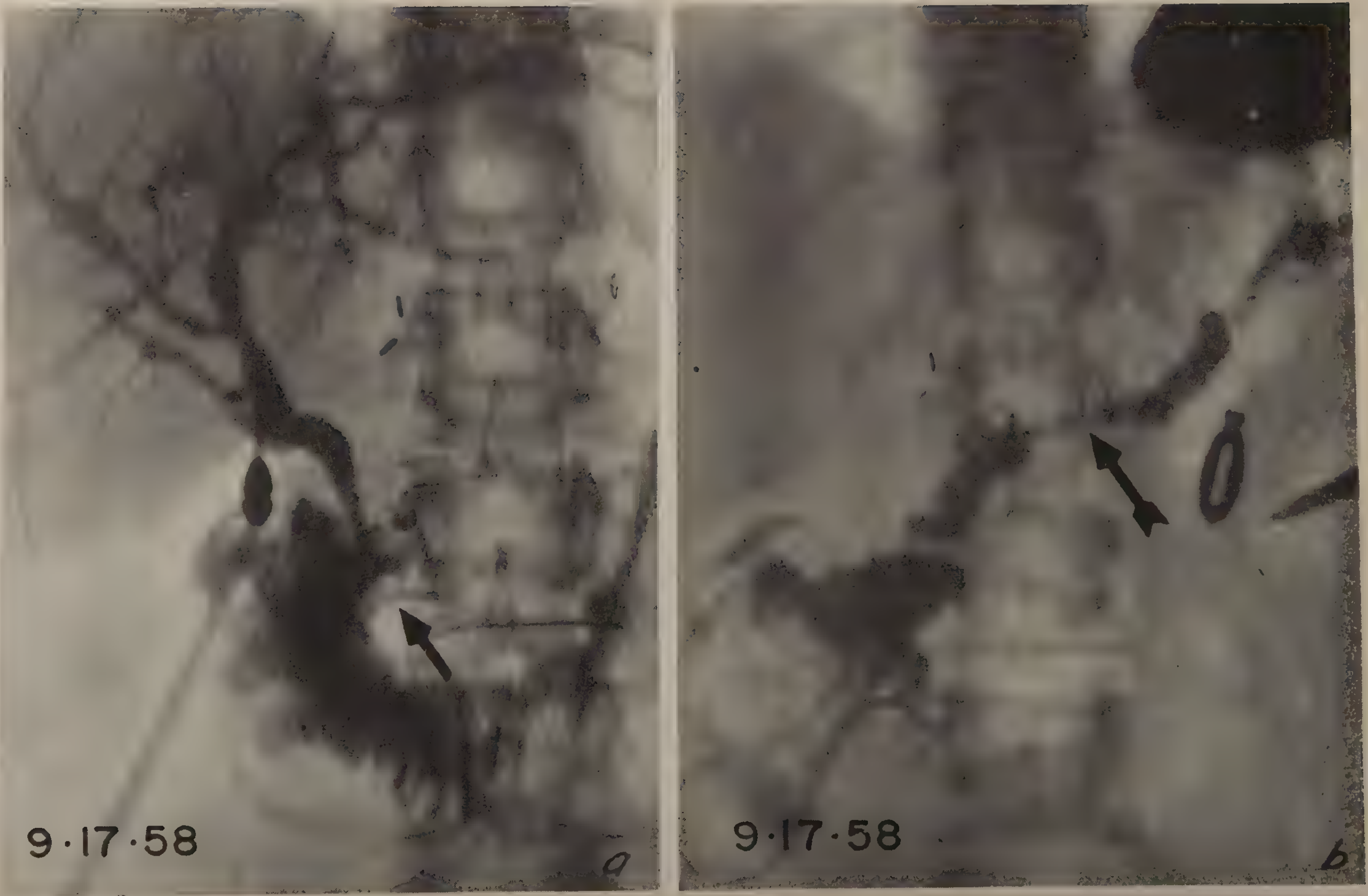


FIGURE 16. Demonstration of partial stricture of the pancreatic duct. The patient developed persistent pancreatic fistula following splenectomy. This operative pancreatogram demonstrated partial stricture (one arrow) due to a suture, with marked dilatation of the duct behind the stricture (2 arrows).

indicated if the duodenum and pancreas are edematous and markedly swollen. If sphincterotomy is performed and the pancreatic duct intubated, pancreatography should be delayed for about one week, until the patient has recovered from the operation. The tube that is inserted into the duct of Wirsung should fit loosely, permitting excessive radiopaque solution to flow out

FIGURE 17. Demonstration of obstruction and stricture of the pancreatic duct at operation, and the effective drainage produced by a "split" pancreaticojejunostomy. Operative cholangiogram (*a*) demonstrated by reflux obstruction of the pancreatic duct 2 cm. above the papilla (arrow). Following sphincterotomy, an operative pancreatogram (*b*) demonstrated calculus obstruction and stricture of the pancreatic duct (arrows). The pancreas was split transversely in the body, and the duct on each side anastomosed to a jejunal limb. Injection into a plastic tube (*c*) leading from the duct of Wirsung showed ready passage of dye around the obstruction into the body of the pancreas and out through the proximal tube, which passed through the jejunal limb. Injection of the distal tube (*d*) lying in the jejunal limb visualized the tail. Simultaneously, injection of the tube lying in the body of the pancreas showed complete obstruction of the main duct in the head of the pancreas (white arrow). This demonstrated a ball-valve type of obstruction in the main pancreatic duct. (See pp. 844–845.)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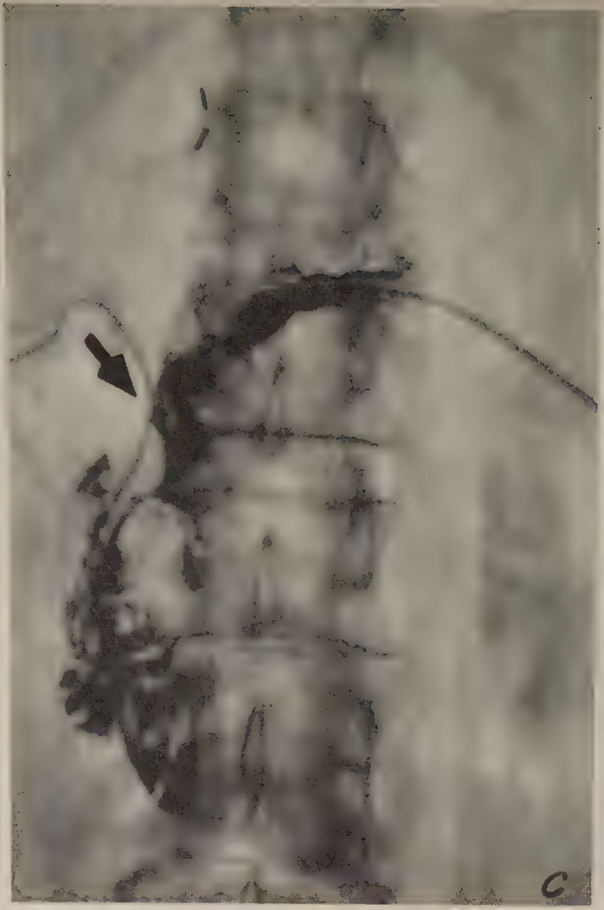
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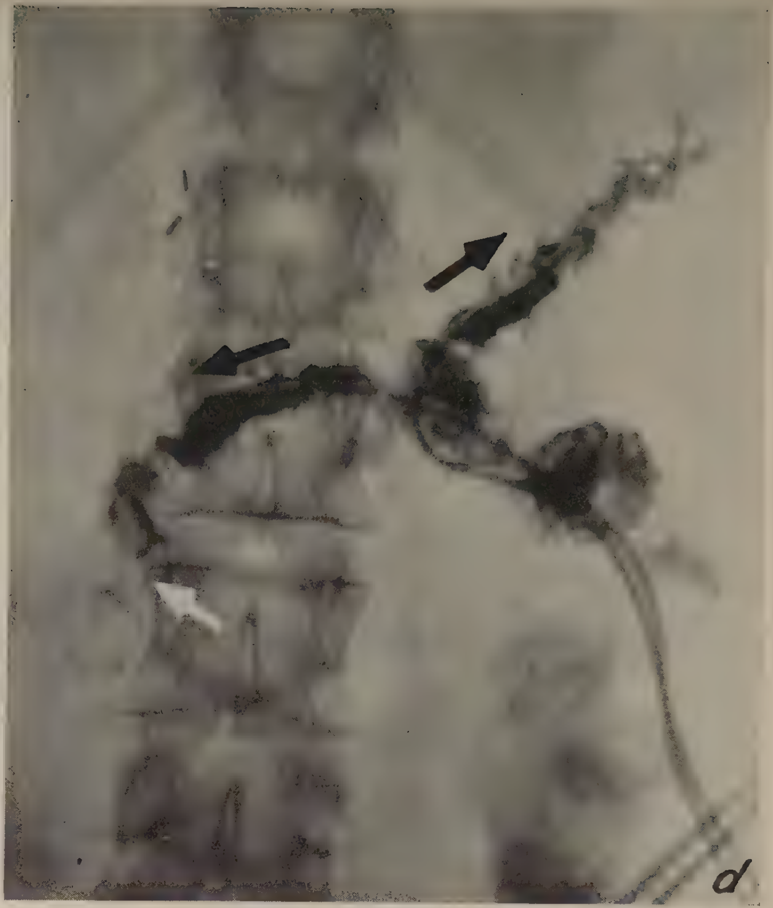
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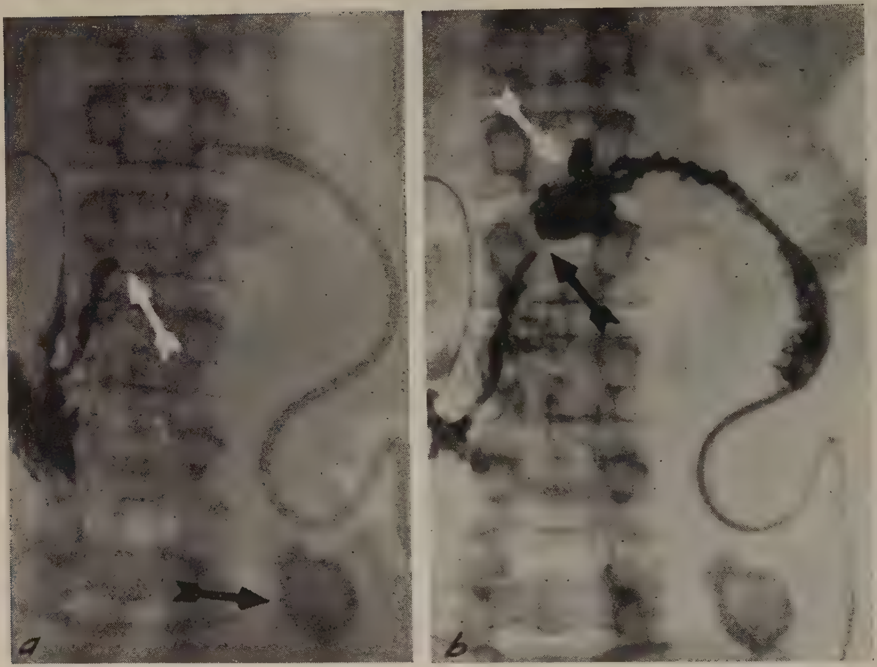

FIGURE 18. Demonstration of pancreatic duct obstruction treated by caudal pancreaticojejunostomy. In this patient the tail of the pancreas had been completely destroyed by necrotizing disease. Pancreatographic study (*a*) through a plastic tube in the duct of Wirsung, showed complete obstruction (arrow). However, a study (*b*) through the tube lying in the pancreaticojejunal anastomosis showed that the obstruction was due to an incomplete stricture (black arrow), since the radiopaque solution passed down into the duodenum. A small pseudocyst (white arrow) was present distal to the stricture.

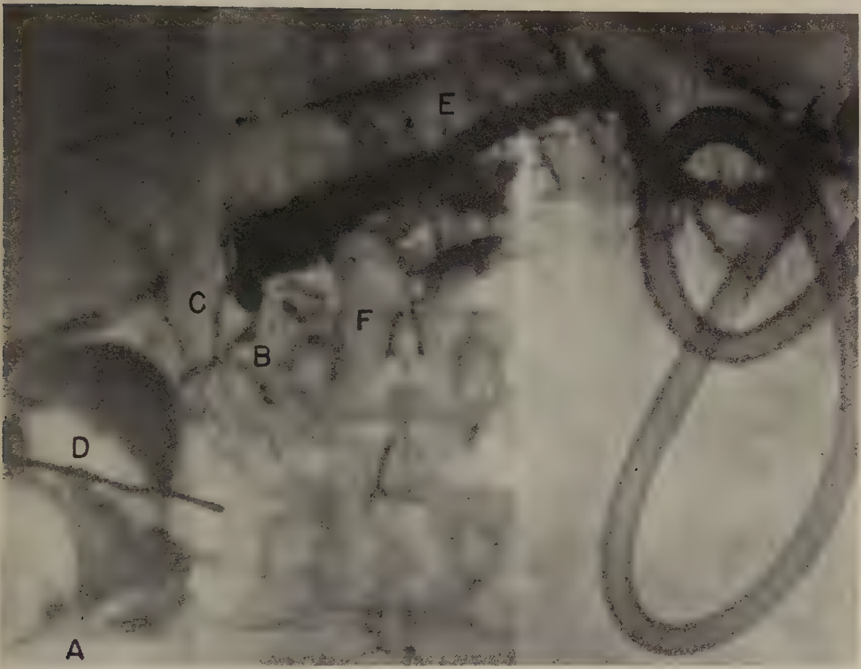

FIGURE 19. Obstruction of the main pancreatic duct by a small cancer of the head of the pancreas. This study through a tube (*A*) lying in the duct of Wirsung, showed obstruction at (*B*) just above the junction with the accessory duct (*C*). A probe (*D*) was inserted into the accessory duct to prevent too rapid loss of the injection fluid. Note the hugely dilated distal duct (*E*) and the faint outline of the superior mesenteric vein (*F*) due to erosion of the tumor into it.

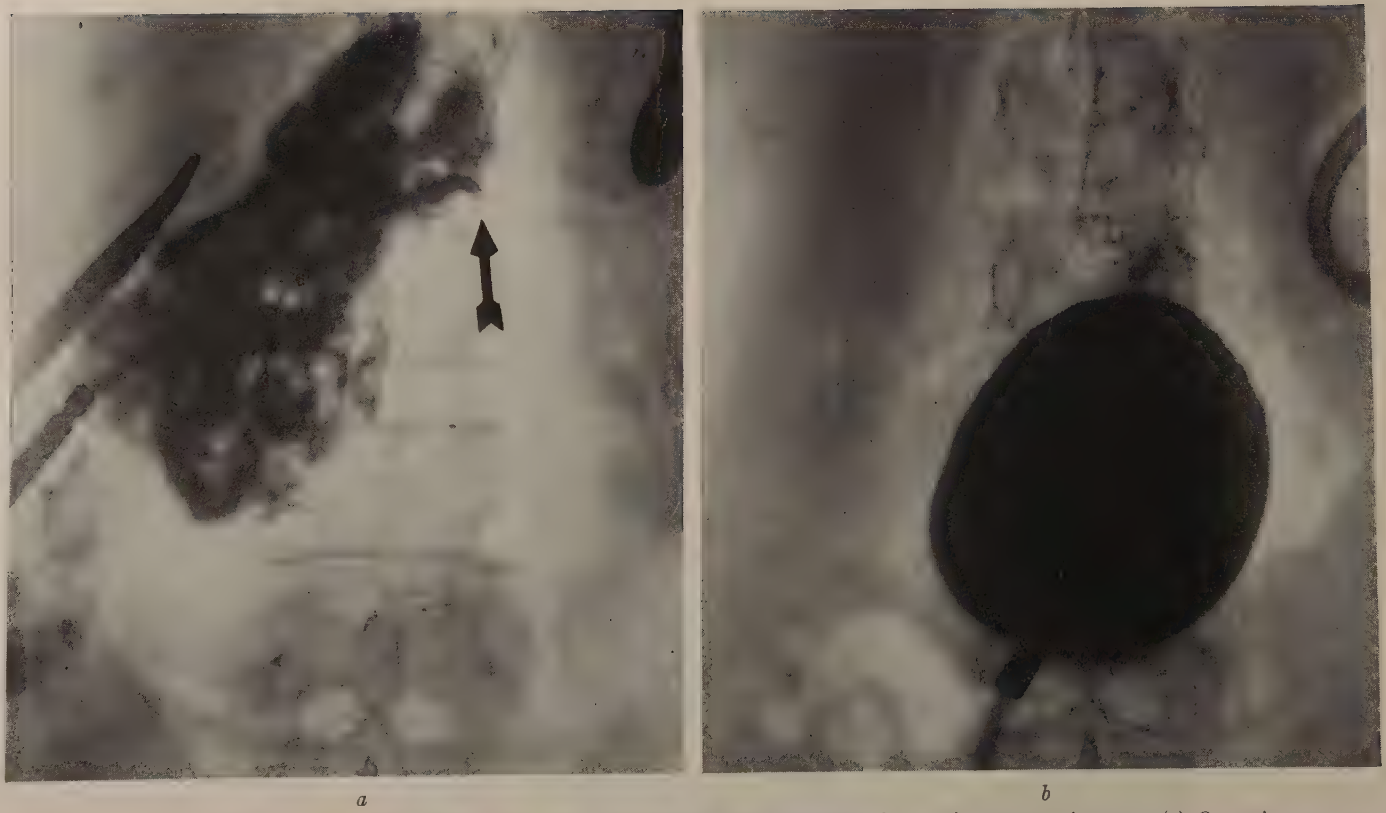

FIGURE 20. Demonstration of complete absence of connection between main pancreatic duct and a mesenteric cyst. (*a*) Operative pancreatogram showed complete obstruction of main duct (arrow) at site of a previous cystogastrostomy. Note complete opacification of the head of the pancreas due to an acute inflammatory process. A large mesenteric cyst was opacified (*b*) and was drained since it was not connected to the pancreatic duct system.

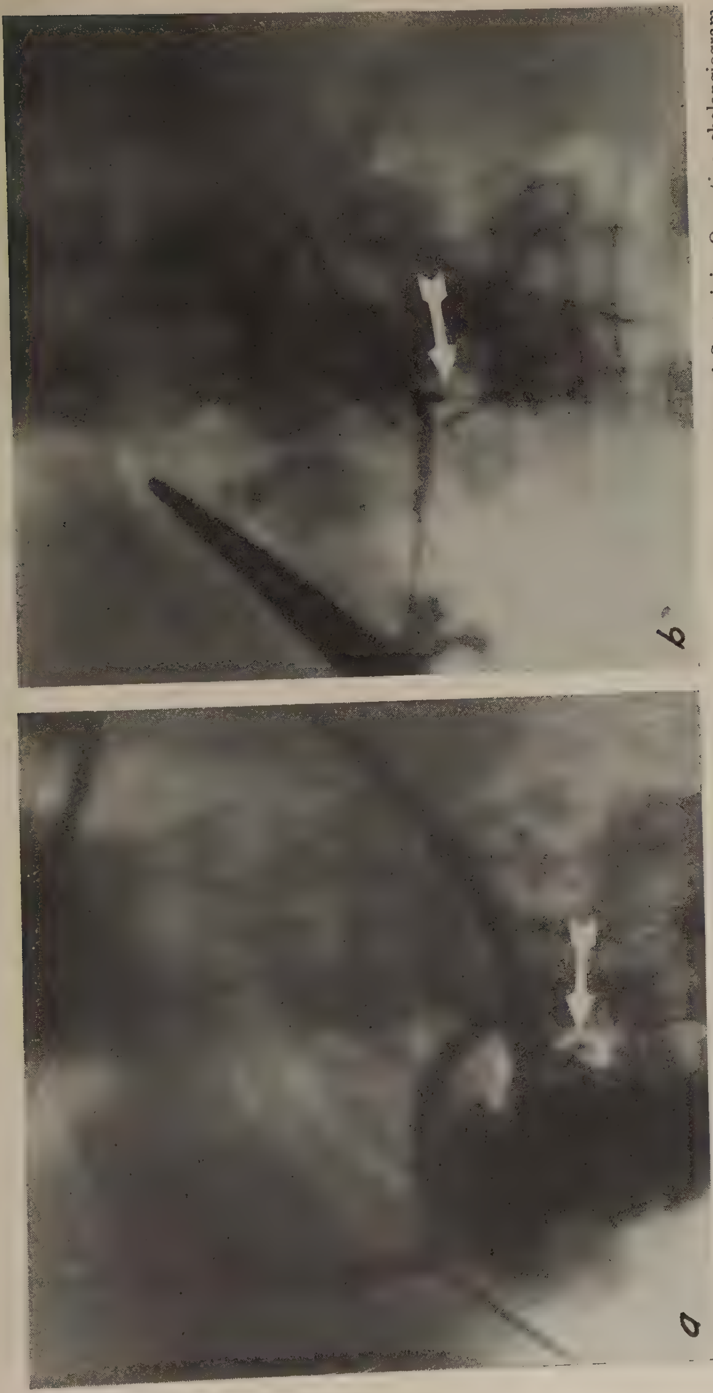

FIGURE 21. Demonstration of obstruction of main pancreatic duct by injection of accessory duct of Santorini. Operative cholangiogram (*a*) showed obstruction of the duct of Wirsung by reflux (arrow). Injection through the accessory duct (*b*) demonstrated the point of obstruction of the main duct (arrow).

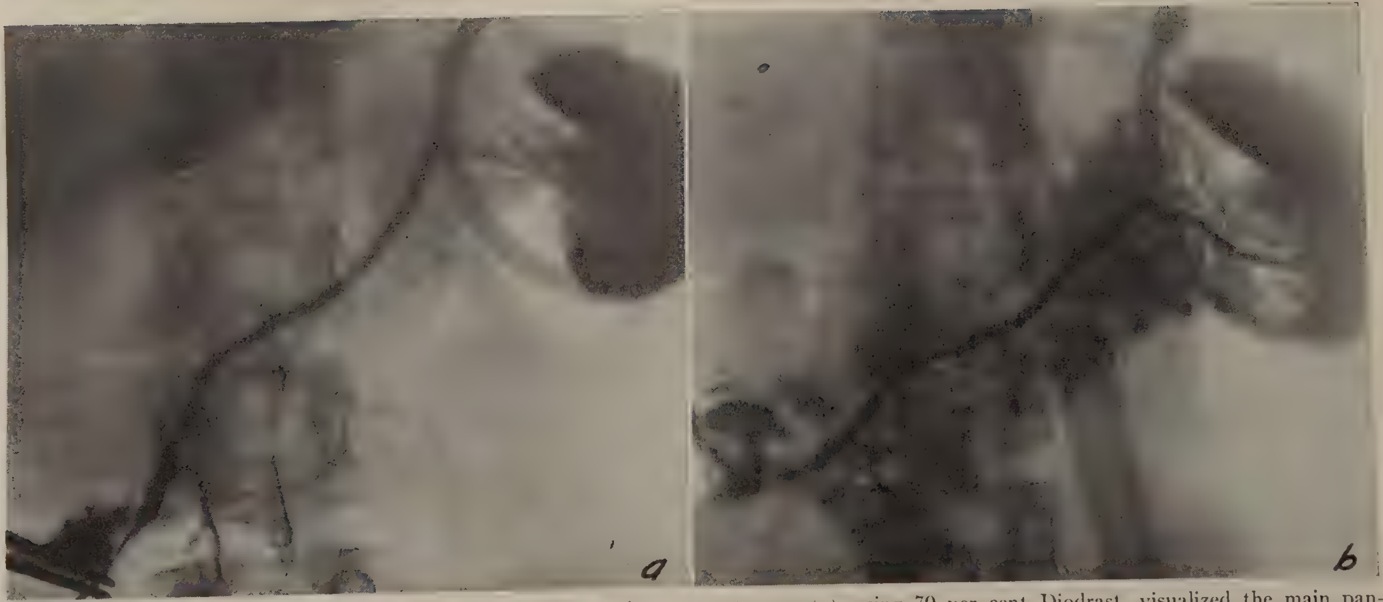

FIGURE 22. Deliberate opacification of the pancreas. Operative pancreatogram (*a*), using 70 per cent Diodrast, visualized the main pancreatic duct. After 10 min., injection of more Diodrast (*b*) opacified the acinar tissue through the increased permeability that resulted from the transient inflammatory reaction produced by the solution.

easily. If the tube is inserted too far, only the tail of the pancreas takes the brunt of the injection and may react severely.

Following operation, the patient should always be treated for 3 days as a case of acute pancreatitis, by nasogastric suction, and by administration of atropine (or Banthine), intravenous fluids, and electrolytes. Postoperative pancreatographic studies should be made only on a patient who is starved overnight and who has received, 1 hour before the study, 50 mg. Banthine and an antihistamine drug as precautions against possible sensitivity to the radiopaque solution.

The ideal radiopaque solution should produce no reaction when injected into the pancreatic ducts. Such a solution has not yet been found, although search is continuing.

Summary

Pancreatography has been found to be of value in determining the variations in the normal anatomy of the pancreatic duct system, in elucidating the pathological process that follows an attack of acute pancreatitis, and in determining the type of operative procedure necessary to overcome the complications of the disease. A new technique also has been developed for opacifying the pancreas deliberately.

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EXPERIENCE WITH THE AVOIDANCE OF ALLERGIC REACTIONS TO PYELOGRAPHIC MEDIA BY THE USE OF ANTIHISTAMINE DRUGS

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All contrast media used for excretory pyelograms evoke undesirable side reactions in some patients. Many are mild and transient reactions, such as flushing, a feeling of warmth, metallic taste, arm pain, nausea, and vomiting. The more serious side reactions include urticaria, asthma, and shock; on rare occasions these result in death. Recently new compounds have been developed that consistently yield pyelograms of excellent quality and also appear to evoke fewer reactions than compounds earlier available.[1, 2]

I recently collected data on the occurrence of severe reactions from members of the American Association of Genito-Urinary Surgeons, Boston, Mass. The purpose of the survey was to determine, from the experience of these urologists, the value of tests for predicting reactions, as well as to discover the prevalent attitude on the value of antihistamine drugs in their prevention. A report of this survey will be published in the proceedings of the association. TABLE 1 shows the data obtained from the survey.

The majority of those reporting expressed some degree of enthusiasm regarding the lack of reactions that have occurred with the new agents, yet there is about a 1-in-500 over-all incidence of severe reactions, and none of the compounds is free of this risk.

The death occurred in a case where 1 cc. of Hypaque was introduced intravenously as a test and no reaction occurred. The final injection was given 45 min. later and, within 5 min. the patient had a circulatory collapse. Oxygen, intravenous fluids, and Neo-Synephrine were administered and, finally, cardiac massage by the open method was done. An authority[3] in the field of allergy research has informed me that this death probably was not due to an antigen-antibody or histamine release mechanism for the reason that no reaction of an allergic nature was evoked by the preliminary test dose. It was postulated that a serotonin or a direct cellular histamine or some other chemical release might have been the basis for the reaction, and that it probably would not have been prevented by antihistamine injection. Another possibility is that the newer urographic media may have some direct depressing effect upon the cardiovascular system similar to the effects of Diodrast. Various investigators[4, 5] have demonstrated that Diodrast is a potent vasodilating agent that produces a fall in blood pressure and changes in the arterial pulse contour. The Diodrast reaction, particularly in humans, is suggestive of a parasympathetic discharge such as would occur, for example, after the administration of acetyl-beta-methylcholine. The effects are a drop in blood pressure, bradycardia, nausea, flushing, cough, dyspnea, and sweating. Gordon *et al.*[6] (1950), who studied the effects of Diodrast in animals, were unable to prevent their occurrence with atropine, vagotomy, or tetraethylammonium and concluded that the peripheral

TABLE 1
DATA OBTAINED FROM SURVEY

No. investigators reporting	Medium	No. of injections	Severe reactions		Deaths
			Allergic	Shock	
41	Hypaque	111,000	150	117	1
12	Miokon	20,000	13	15	0
10	Renografin	13,000	2	4	0
63		144,000	165	136	1

effects are probably exerted directly upon the smooth muscle of the vessel walls. These investigators were unable to prevent the "Diodrast reaction" in animals with Pitressin, sympathomimetic drugs, or epinephrine. In fact, they found that the secondary vasodepressor action of epinephrine potentiates that of Diodrast and suggested that epinephrine might be harmful rather than beneficial in treating this type of reaction clinically. Pendergrass[7, 8] estimates the incidence of fatal reactions as 8.6 per million urograms.

In our survey forty-one reported the use of some test procedure for predicting sensitivity to the compounds. Many employ intradermal or conjunctival testing, yet only two believe that these tests have any value. It appears that these tests are performed not so much for patient protection as for legal protection of the doctors. Pendergrass reported that sensitivity tests were negative in about two thirds of the cases that died. It should be pointed out that most of the tests in question are tests of allergic sensitivity and that they are probably reliable indices of this type of reaction. However, the shock reaction, which often is associated with fatality, is probably not an antigen-antibody response and so would not be predictable by the usual allergy tests.

Many of the urologists canvassed in our survey inject 1 cc. or less of the contrast medium as a test for reactions, and the majority believe that this is a reliable indication. Yet 14 men point out that this is completely unreliable. In this connection 29 of the 61 fatal reactions reported recently by Pendergrass *et al.* (1958)[8] occurred in patients to whom intravenous test doses of 1 cc. of contrast medium were given and no reactions were observed. Pendergrass also reports that 3 of the fatal reactions occurred in persons administered less than 2 cc. of the contrast medium.

These observations fit into the concept that the shock reaction may be due to a drug idiosyncrasy or intolerance and not an immunological mechanism. Idiosyncrasy has been defined[9] as denoting a qualitative alteration in the response of the individual to the pharmacological or toxic actions of a drug. Some patients experience the usual therapeutic or toxic effects of a drug at dosage levels either much lower or much higher than that usually required to produce these effects. If shock reactions are indeed due to idiosyncrasy, then a 1-cc. dose might not evoke a severe reaction in one patient, while the same amount might be fatal in another.

Results obtained by our group with antihistamine drugs for preventing reactions have been varied. Nearly every person who reported the use of antihistamines expressed a belief that they are distinctly valuable. Those who administer the drugs orally appear to be the least enthusiastic as a group, yet some of these have a high regard for the method. It would appear that oral premedication has been most effective when employed in fairly large doses given at least 1 hour before the injection of the contrast medium. One member of our group reported that he gives 100 mg. of pyrobenzamine orally to all patients who have a history of allergy, and that he has observed excellent and uniform protection from reactions in these patients.

While visiting England in July, 1957, I made the rounds at The London Hospital, where it was revealed that antihistamine premedication is employed in all patients who have a history of allergy. Such patients are given 25 mg. of Phenergan by mouth the night before and another 25 mg. the morning of the injection; an intramuscular injection of 25 mg. is then given 20 min. prior to the injection of the urographic medium (Hypaque). Intramuscular injection of Phenergan is preferred to intravenous as it is thought to afford a longer period of protection. When this medication has been employed in patients who give a history of allergy there have been no reactions.

In our survey, the urologists who have employed antihistamine drugs intravenously have had better results in the aggregate than those who have given them orally. There are 2 methods of administering the compounds intravenously; most popular is that of mixing the antihistamine with the contrast medium for simultaneous injection. In the other method the antihistamine agent is administered intravenously 3 to 5 min. before giving the iodine compound. Investigators in the field of allergy state that the latter procedure offers greater protection against histamine release than does simultaneous injection; clinical experience would appear to bear out that assertion. Our members who have given antihistamine drugs simultaneously with the injections of the contrast media have found a lessened incidence of reactions; however, a few have observed that reactions occurred often enough to raise a doubt as to the value of the method.

Among those who have administered the drugs intravenously as a premedication there has been unanimous agreement concerning the value of antihistamine protection. The largest series reported was that of my colleagues,[10] who employed 50 mg. Benadryl in 1 cc. of water intravenously as a premedication in more than 3000 cases where 70 per cent Urokon was used. These patients, observed at the Wayne County General Hospital, Eloise, Mich., showed only 2 allergic reactions and no shock reactions. There was 1 mild urticaria and 1 severe urticaria with bronchial spasm that was relieved by adrenalin. One can only speculate upon the nature of the reaction that might have occurred in this patient had not Benadryl been competing for histamine that was released by the iodine compound. In this connection, some investigators[11] believe that anaphylactic or allergic reactions cannot be entirely avoided by the administration of antihistamine drugs since it has been shown experimentally that maximum effective doses of these drugs do not completely eliminate the action of injected histamine.

One of our members reported that he gives 10 mg. of Chlor-Trimeton intravenously as a premedication in all cases with a history of allergy and has observed

TABLE 2

RESULTS WITH PREMEDICATION COMPARED WITH CONTROLS

Premedication	No. of cases	Medium	Percentages		
			Allergic reactions	Side effects	
			Urticaria and dyspnea	Nausea	Vomiting
Controls, no antihistamine	364	Hypaque	3.1	13	2.2
	350	Miokon	2.0	22	3.7
12 mg. Phenergan, I.V.	543	Hypaque	0.5	2.8	0.0
	417	Miokon	0.5	8.9	0.5

only 1 reaction (mild) in this group of patients. Another has given the same premedication in 600 cases with histories of allergy, and only 1 patient had any reaction—a single hive.

Some of the lesser reactions such as nausea and vomiting and arm pain appear to be unaffected by Benadryl or Chlor-Trimeton. Lapides[12] compared the incidence of these reactions in the 70 per cent Urokon cases and found that nausea and vomiting occurred just as often in the premedicated patients as among those who had Urokon alone.

At the University Hospital, Ann Arbor, Mich., we are observing a series of cases that are premedicated with Phenergan, an antihistamine drug which has a profound antiemetic property. Twelve milligrams of Phenergan is administered intravenously about 5 min. before the pyelographic medium is injected. Nine hundred and sixty patients have been treated in this manner and there appears to have been a significant decrease in the occurrence of nausea and vomiting. TABLE 2 indicates the observations made on a control series, as well as the cases premedicated with Phenergan.

Together with the marked decrease in occurrence of nausea and vomiting there has been observed a significantly decreased incidence of allergic reactions. However, our Phenergan series at the University Hospital has displayed a distinctly greater occurrence of reactions than has the Benadryl series at Wayne County General Hospital where only 2 very minor allergic reactions have occurred in more than 3000 injections. The low incidence of reactions in the latter series is all the more impressive considering the fact that 70 per cent Urokon has been used in all the cases. Qualitative differences in the hospital populations of the 2 institutions may account in part for some of these differences. In both institutions the contrast media are administered by members of the resident staff who observe the patients carefully and record data on every case. We now plan to use Benadryl at the University Hospital together with Hypaque and Miokon on alternate cases to determine whether the same protection from all types of reaction will prevail among the University Hospital population with these less toxic agents. The results of this study will be published.

Most of the reactions that have been observed in the University Hospital Phenergan series have been of a very mild nature and have given no cause for alarm. However, there have been 4 cases of a more severe nature that should be described in detail since some of the particulars may be of value in a long-term study elucidating the nature of severe or fatal reactions. The statistically minded will find interesting the fact that the reactions in question occurred in the last 100 cases of our series, all within a 3-week period.

The first patient of the 4 showing severe reactions is a 17-year-old female who was being studied because of recurrent urinary-tract infection. Her general physical condition was good and her renal function, determined by P.S.P. and creatinine tests, was normal. There were a few patch areas of atopic eczema of the skin, and blood counts were normal.

After the intravenous injection of 0.5 cc. (12.5 mg.) of Phenergan she received 28 cc. of 50 per cent Hypaque. A very slow injection of the contrast medium was employed because of a history of atopic eczema since early childhood, multiple food intolerances, and various allergies to plant pollens and dust. She had never had a complete allergic investigation with skin tests.

Shortly after the injection was finished she complained of nausea and, 1 min. later, vomited. Two minutes later she had a sensation of swelling of the lips and throat and difficulty in breathing. No swelling could be observed by the attending physician and auscultation of the chest revealed normal breath sounds, good air exchange, and normal thoracic excursions. The pulse was 92 and blood pressure 98/58. Within an additional 2 min. she began to writhe in pain and complained of a severe burning sensation extending from the throat to the symphysis pubis. The pain rapidly increased in severity and concentrated in the suprapubic area. Catheterization of the bladder was done—60 cc. of fluid was obtained—but the pain was not relieved. At this point the femoral pulsations were found to be good, the bowel sounds were normal, and the blood pressure was 128/68. Ten minutes after completion of the contrast medium injection the abdominal pain began to subside but the patient developed circumoral pallor, conjunctival injection, a red blush over the face and neck, and urticarial lesions of the chest, arms, and legs. Benadryl, 50 mg. in 5.0 cc. of water, was administered intravenously, and within 2 min. the cutaneous lesions had almost completely disappeared. At 20 min. after injection of the contrast medium the patient was resting quietly but complained of a chill, weakness, and general malaise. At 80 min. the only residual symptoms were a cold sensation and drowsiness. This somnolence was thought to be due to the soporific action of the antihistamine agents.

This patient had been examined by the Allergy Section of the University Hospital since the reaction noted above, and skin tests have demonstrated a sensitivity to the iodine compound that was used.

The next patient is a 30-year-old woman who was being investigated for ascites. The past history included no known allergies, although she was reported to have been treated in 1954 for a "nervous dermatitis" with eczematoid features, which began with urticaria and edema of the face and eyelids and was treated with cortisone. Shortly after injection of 12.5 mg. of Phenergan she coughed but displayed no other reaction. After the injection of 30 cc. of 50 per cent Miokon she complained of nausea and experienced some retching but no emesis. The development of a burning mid-chest pain was not accompanied by abnormal findings on examination of the chest; at that time, the blood pressure was 100/70 and the pulse 88. A few minutes later there was a diffuse red flush over her body and she had a hot sensation over the body, the face, and neck. There then developed marked pruritis but no urticarial lesions or hives. Benadryl, 50 mg. was given intravenously, and the symptoms abated. About 15 min. after the injection of the contrast medium additional symptoms of dizziness, general malaise, and tightness of the skin of the face were mentioned. Shortly thereafter puffiness of the upper face and eyelids (angioneurotic edema) was in evidence. An additional 50 mg. of Benadryl was given intravenously with no significant effect. One hour after injection of the contrast medium there occurred a mild intermittent shaking chill and numbness of the face. The patient's vital signs remained stable and, after 12 hours of sleep, she had no residual symptoms. Later, this patient was investigated by our Allergy Service and the results of tests of sensitivity to the contrast medium were negative.

The third patient was a 27-year-old woman who was investigated because of a chronic urinary-tract infection. She had had a nephrectomy 5 years before for a congenital anomaly of the kidney. There was a history of intolerance to sulfa drugs, which produced nausea but no other reactions. No allergies were reported by the patient and her normal blood pressure was 102/76.

This woman had premedication with 12.5 mg. of Phenergan intravenously. She received 30 cc. of 50 per cent Miokon and shortly thereafter became diaphoretic and pale and complained of a cold sensation. Her pulse became weak and rapid, although the blood pressure was 130/70. She was given 0.3 cc. of adrenalin 1:1000 solution and her symptoms gradually abated. About 30 min. after the reaction began her blood pressure was 98/60 and she complained of a sensation of coldness; no other symptoms occurred, and she felt well 3 hours later.

The fourth patient was an 8-year-old boy who had chronic glomerulotubular nephritis. His premedication consisted of 0.25 cc. (6 mg.) of Phenergan, and he was given 15 cc. of 50 per cent Miokon. Following this he exhibited a red flush of the head and neck and, 2 min. later, developed a severe occipital headache. The blood pressure at this time was 142/82. The boy was sat upright and was given spirits of ammonia to inhale; the headache subsided within a few minutes and the blood pressure dropped to 112/68. He then became sleepy and slept most of the day. The following morning he appeared to have no symptoms. There was no history of allergy in this case.

The first of these cases was doubtless an allergic reaction to the pyelographic medium. It abated promptly following intravenous Benadryl. The second case appears not to have been allergic, for the patient was not benefited by Benadryl administration and was not found (by skin tests) to be sensitive to Miokon. The other two reactions were certainly not allergic in nature; one probably was merely vertigo while the last, with headache and slight elevation of the blood pressure, remains unexplained.

The protective value of antihistamine drugs in patients who have had previous reactions has been demonstrated in but few reported cases. Olsson (1951)[13] reported on "a number of cases" who had experienced reactions to the same medium; these patients, when protected by 20 mg. of Benadryl, suffered no discomfort. This investigator expressed the opinion that 20 mg. of Benadryl administered intravenously is adequate protection against any amount or repeated injections of the medium. My information, obtained from experts in the field of allergic research, is that Benadryl should be administered intravenously in the amount of 50 mg. if it is to afford maximum effective protection when used as a premedication.

A significant case in the category of protection was reported to me by Melvin Figley, of the University of Washington Medical School, Seattle, Wash. While at Ann Arbor, Figley supervised all the arteriography performed at the University Hospital. He observed a severe shock reaction following arteriography with 70 per cent Urokon in a young man examined for a vascular anomaly. A repeat arteriogram became necessary at a later date, and 50 mg. of Benadryl was administered intravenously a few minutes before the Urokon injection; no reaction occurred.

Another similar experience was observed in a student at the University of Michigan who had a severe allergic reaction following pyelography with Hypaque. Later, another pyelographic study was carried out with Hypaque but, this time, intravenous premedication with 50 mg. of Benadryl was used and the patient had no reaction.

A third case in my experience was a dramatic error, fortunately not fatal. The patient had her ureter injured during a laparotomy for pelvic neoplasm; this was successfully repaired. During check-up pyelograms she went into severe shock following Miokon injection and apparently was saved by prompt oxygen administration by an anesthetist who chanced to be present at the time. Later, the patient was seen in the Urology Clinic for check-up and was again given Miokon by a resident surgeon who was not informed of the reaction that had occurred 3 months before. Again she went immediately into a severe state of shock and again was apparently saved by the fortuitous presence of an anesthetist who administered artificial respiration and oxygen. A few months later she was re-examined. This time 50 mg. of Benadryl was given as premedication; Hypaque was employed as the medium and there was no reaction. Subsequently the patient was examined on the Allergy Service and was found to react severely to skin tests with both Miokon and Hypaque.

A disadvantage of antihistamine administration is the soporific effect that sometimes occurs. Occasionally patients become quite sleepy when these drugs are administered by any route. This effect has no great disadvantage in the hospitalized patient but can be disturbing or even potentially dangerous to the ambulatory patient, particularly one who has driven an automobile to the X-ray laboratory. When ambulatory patients are given these drugs they should be observed for a short period of time and, if sleepy, should be given amphetamine to counteract the somnolent effects. Thereafter they should not drive a motor car for several hours.

Discussion

It appears evident that there are at least two distinct types of severe reactions that are evoked by intravenous administration of urographic media.

One is an antigen-antibody reaction that can be severe in nature and probably fatal in certain cases. This allergic reaction can probably always be predicted by standard allergy tests for specific sensitivity; it can generally be prevented by antihistamine drugs and can be ameliorated or terminated by antihistamine therapy.[14-16]

The second type of reaction, the so-called shock reaction, is not allergic in nature. This reaction, which also may be fatal, probably is due to drug idiosyncrasy; it is not predictable by known methods of preinjection testing and does not appear to be responsive to antihistamine or other chemical methods of treatment. Whether its occurrence can be prevented by premedication is not known.

The study reported in this article has revealed that the urologists who have employed antihistamine drugs to avoid or diminish reactions with urographic media are convinced of the value of these drugs. The reports suggest that oral administration affords the least protection and that premedication by intravenous injection is better than the simultaneous administration of the antihistamine with the iodine compound.

My studies with Phenergan as a premedication in nearly 1000 cases have demonstrated that this compound will reduce substantially the incidence of allergic reactions to the urographic agents that have been tested. Also, the antiemetic properties of Phenergan appear to have reduced the incidence of nausea and vomiting. However, a few reactions of a severe type were observed in the Phenergan series. In comparison, the Benadryl series by colleagues in a nearby hospital suggests the possibility that this antihistamine may possess protective properties that are of a superior order for, among 3025 cases, there were only 2 allergic reactions and no shocklike reactions. It is possible that this may be related to the atropine effect of Benadryl, which is greater than the atropine effect of Phenergan. It is also possible that the dosage of Benadryl bears an important relation to its usefulness in this connection. Hart *et al.* (1958)[17] recently reported a series of more than 4000 cases in which a variety of urographic media was used and in which Chlor-Trimeton as well as Benadryl was used to prevent reactions. These investigators found that the antihistamine drugs were beneficial in reducing incidence and severity of reactions, but did not eliminate them entirely. One of their patients, who had Benadryl simultaneously with Urokon, suffered a shock reaction. The patients were given only 10 mg. of Benadryl, which appears to be a very small dose.

My observations suggest that Benadryl in proper dosage and administered intravenously may afford maximum protection against not only allergic but also the so-called shock reactions that occur with urographic media. Whether all fatal reactions or, indeed, all shocklike reactions could be eliminated by this means may be determined only by the observation of an enormous number of cases: it should be recalled that Pendergrass estimated the incidence of deaths at 8.6 per million urograms. It is interesting to observe that none of the fatal cases listed by Pendergrass was reported to have had antihistamine premedication.

The evidence in favor of utilizing antihistamine premedication appears to suggest that serious reactions and deaths from reactions to urographic media can be reduced, if not entirely eliminated. Only the widespread use of these preventive techniques will reveal their ultimate worth.

Roentgenologists and urologists in the United States could determine the ultimate value of antihistamine protection within the course of one or two years if a large number of them would administer these drugs as routine and report the occurrence of any adverse reactions or deaths to their respective societies. Only by obtaining the record of an enormous number of cases can this important matter be settled. This objective is worthy of our professional effort.

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SIMULTANEOUS PYELOGRAPHY AND CHOLECYSTOGRAPHY

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More than one third of a century ago, the combined efforts of the chemist, the pharmacologist, and the radiologist produced a contrast medium that, when intravenously injected, is selectively excreted by the kidneys, with concomitant roentgen visualization of the entire urinary tract.

In order to produce a satisfactory intravenous urogram a compound must (1) have a sufficiently high iodine content to assure a shadow of density greater than that of the surrounding tissues; (2) be susceptible of excretion by the kidneys, that is, it should be water-soluble or water-seeking (hydrophylic); and (3) be safe when used on human subjects as well as on animals, the most important single consideration or prerequisite of any medication.

The progress made thus far should not persuade us to forget the growing pains experienced by the medical profession at large, and radiology in particular, as intravenous urography came to maturity. We were confronted with the problems of precipitation, preparation of solutions, diffusion through the body fluids, side reactions, and so-called allergic reactions, varying from mild urticaria to nausea and vomiting, respiratory distress, fall in blood pressure, circulatory collapse, and the infrequent but nevertheless tragic complication of death—immediate or delayed. These experiences prompted a continuous search for media with improved diagnostic value and greater safety, as well as for methods and techniques helpful in reducing and combating side reactions.

To attempt to name the multitude of preparations that have since appeared, been tested, and discarded would serve no purpose at this time. Suffice it to say that great strides have been made and that contrast media that are close to the ideal are now at our command.

Hypaque and Renografin are two products practically identical in chemical structure, iodine content, and pharmacological properties as well as in the quality of the shadow they produce radiologically. With them, urinary tract visualization is optimal and of excellent diagnostic quality, and administration is easy. The contrast medium is well tolerated by the patient, with minimal side reactions and, insofar as our experience indicates, with total safety.

We are fully cognizant of the fact that further progress must take place and that when better contrast media are produced they will replace the materials now available.

Biliary tract visualization has been less dramatic, being achieved step by step. In 1924, Graham and Cole succeeded in adding bromine to a phenolphthalein radical; later, they added iodine to the phenolphthalein radical (tetraiodophenolphthalein), producing a compound of greater safety. Administered intravenously, this produced adequate gall bladder visualization. Soon after, the much less toxic oral preparation of the tetraiodophenolphthalein group appeared, and remained practically unchallenged until 1940, when Priodax became available. These media, with a 2-iodine atom in their molecular structures, produced gall bladder visualization without bile duct visualization.

In 1949, following clinical studies in our Department of Radiology, Telepaque, a 3-iodinated molecular compound, rapidly replaced all of its predecessors. Orally administered, it produces excellent gall bladder visualization and, for the first time, consistent visualization of the ducts along the outflow path; at times it produces by reflux, visualization of the hepatic ducts. In 1953, Schering of Berlin, Germany, and E. R. Squibb & Sons, New York, N. Y., introduced a 6-iodinated molecular compound, marketed as Biligrafin and Cholografin. Intravenously injected, this resulted in prompt and immediate visualization of the entire biliary tract—bile ducts as well as the gall bladder. Cholografin was soon replaced by Cholografin Methylglucamine, with further improvement in visualization and a marked decrease in toxicity. The use of Cholografin Methylglucamine is accompanied by practically no significant side reactions.

The rapid and dramatic success of intravenous cholangiography has been made possible by the lessons learned through the development and evolution of intravenous urography. The pitfalls and errors and the extensive background of experience at our command as a result of the early difficulties of intravenous urography were telescoped into a period of about one year during the development of intravenous cholangiography.

In a further effort to widen the scope of contrast radiography and to increase the amount of information gained while decreasing the technical work involved, reducing the time needed and, to a certain extent, reducing the amount of radiation to the patient, we have arrived at a technique that will give simultaneous visualization of both the urinary and biliary tracts.

It is felt that this procedure represents a genuine contribution to diagnostic roentgenology giving, as it does, increased information with greatly reduced work. By combining Cholografin Methylglucamine and Renografin a new product has been introduced that permits simultaneous visualization of the urinary and biliary tracts. At the time of our initial studies this compound was known as SH 332; subsequently it was named Duografin. Inasmuch as Cholografin Methylglucamine normally was excreted by the kidneys in at least 50 per cent of the patients examined, this component accentuated the role of Renografin in visualization of the urinary tract by prolonging renal excretion and consequent urinary tract visualization. It was important, therefore, to find an optimal combination of the two media that would give an equal and uniform degree of visualization of both the biliary and urinary tracts.

The results obtained with the first combination of 20 per cent Cholografin Methylglucamine and 40 per cent Renografin were not entirely satisfactory. Later, a combination of equal strength, namely, 30 per cent of each, was tried, with some improvement. Finally, a combination of 40 per cent Cholografin Methylglucamine and 20 per cent Renografin was tried with results that seemed to be eminently satisfactory. At the time of our investigation the combinations tried were called Duografin No. 1, Duografin No. 2, and Duografin No. 3, respectively; the last is now in use as Duografin.

Our efforts were further directed to the determination of the place of this agent in our daily routine, the determination of its indications and contraindications, and the establishment of a standard technique.

Indications

Examination with Duografin is indicated in those patients who require (1) a general check up, (2) a survey of both the biliary and urinary tracts, and (3) a differential diagnosis of ill-defined conditions of the right upper quadrant and abdomen; it is also indicated (4) in patients with complaints referred to the right side anteriorly and posteriorly, but without definite localization; and (5) in the differential diagnosis of masses of the right side.

Contraindications

As in intravenous urography and cholangiography, contraindications are impaired kidney and liver function and a history of untoward reaction to intravenously injected contrast media.

Preparation of the Patient

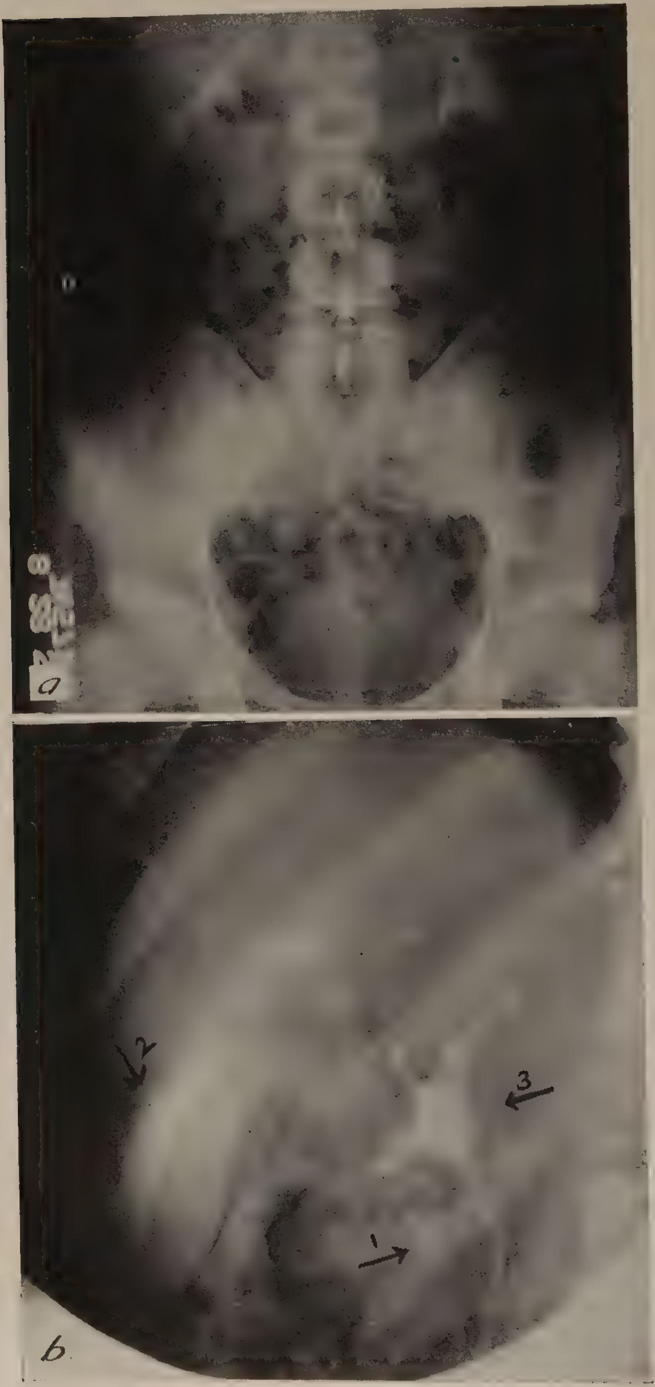
The preparation is essentially the same as for intravenous cholangiography and/or urography. The patient is dehydrated by withholding fluids for at least twelve hours. Cleansing of the bowels is best accomplished by castor oil administered at bedtime.

When the gall bladder is present, at least one meal on the preceding day—supper or, possibly, lunch and supper—should consist of food containing simple fats. This results in drainage of the gall bladder and subsequent better filling with the contrast medium during the examination.

TABLE 1

FINDINGS DURING SIMULTANEOUS VISUALIZATION OF BILIARY AND URINARY TRACTS

No. of cases	Findings
7	Fibrosis of the sphincter of Oddi with proximal bile duct dilatation (3 with normal gall bladder, noncholecystectomized, and 4 cholecystectomized). Four came from the urological service, 3 from the medical.
1	Double gall bladder, that is, discovery of a normal gall bladder after prior surgical removal of a gangrenous gall bladder; dilatation and redundancy of both ureters; retroperitoneal mass compressing the right ureter; urinary bladder calculi.
4	Right hydronephrosis (3 cholecystectomized and 1 normal gall bladder noncholecystectomized).
3	Ptosis or appreciable mobility (or both) of the right kidney in cholecystectomized patients with right-side distress.
1	Absent right renal function in a cholecystectomized patient referred for cholangiography.
1	Horseshoe kidney.
10	Uterine fibroids with compression of the urinary bladder.
11	Anterior enlargement of the prostate.
1	Demonstration of normal urinary and biliary tracts. Barium enema revealed carcinoma of ascending colon, obvious cause of right-side distress.
1	Incidental finding of fractured right transverse process of L-4 (on the urinary-tract film) as cause of right-side pain in a cholecystectomized patient referred for cholangiography.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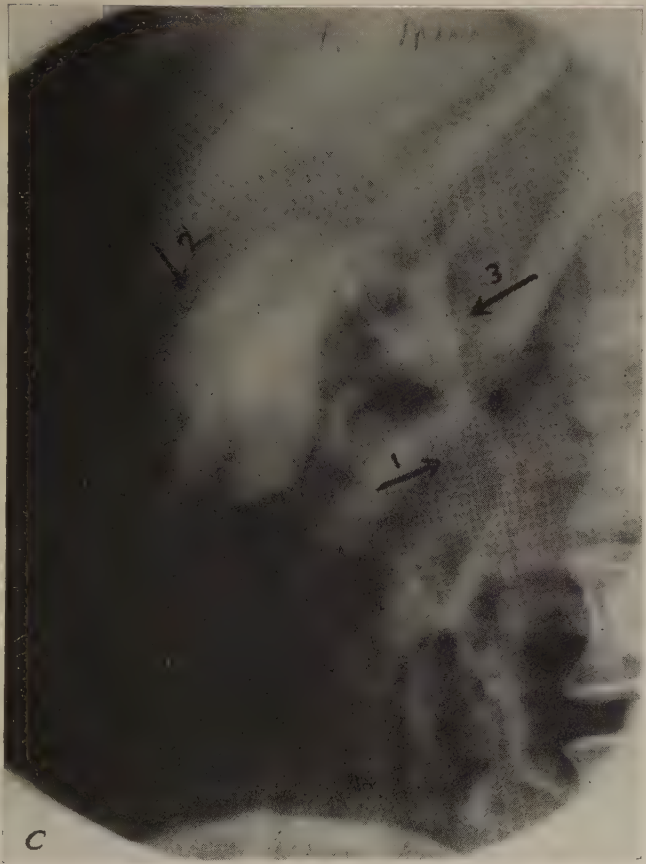


FIGURE 1. Case 1, S.P., August 8, 1958. (*a*) Ten-minute film showing normal urinary tract. (*b* and *c*) Films made at 30 and 40 min. after injection, demonstrating progressive filling of the gall bladder (arrow 2). The ducts (arrow 1) are well visualized with rotation of the patient. Arrow 3 indicates the right renal pelvis.

The examination should be scheduled for early morning. When a delay is contemplated or is otherwise unavoidable, a simple breakfast of toast, butter, and jelly, and a cup of light tea or coffee will tide the patient through a few hours of waiting and will prevent undue distention of the intestines with gas.

In emergency cases, where differential diagnosis is urgently needed, or in the presence of valid contraindications to the preparations outlined above, the patient may be examined without delay upon arrival in the department.

Technique

Essentially, the technique is a combination of that used for intravenous urography and that used for cholangiography. A plain film of the urinary tract is obtained in the usual manner: a 14 × 17 film is made of the kidneys, ureters, and bladder with the patient supine, and a 10 × 12 film of the right upper quadrant for the gall bladder area is made with the patient prone.

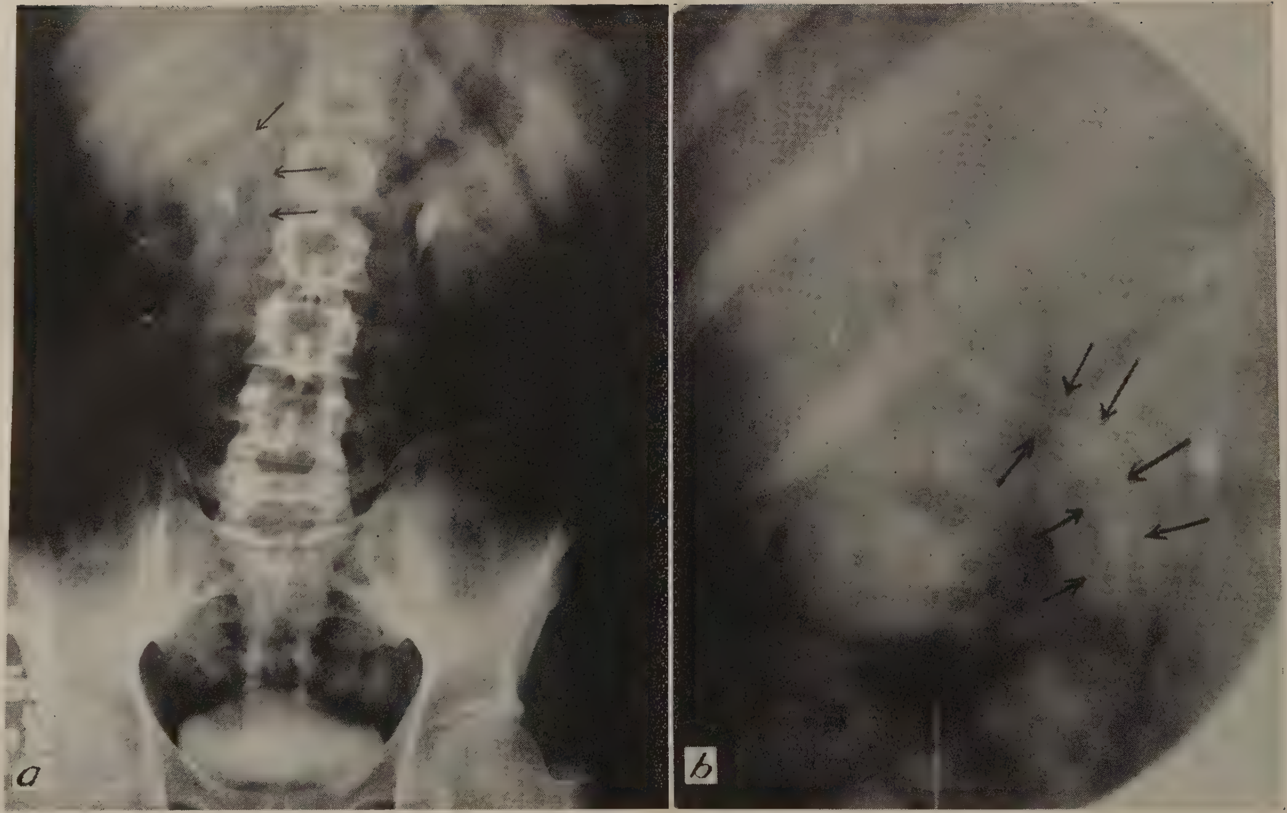


Figure 2. Case 2, W.P., June 11, 1957. (*a*) Film made 15 min. after injection. A normal urogram is demonstrated, except for a defect at the base of the urinary bladder, consistent with anterior enlargement of the prostate. (*b*) Normal hepatic and common bile ducts.

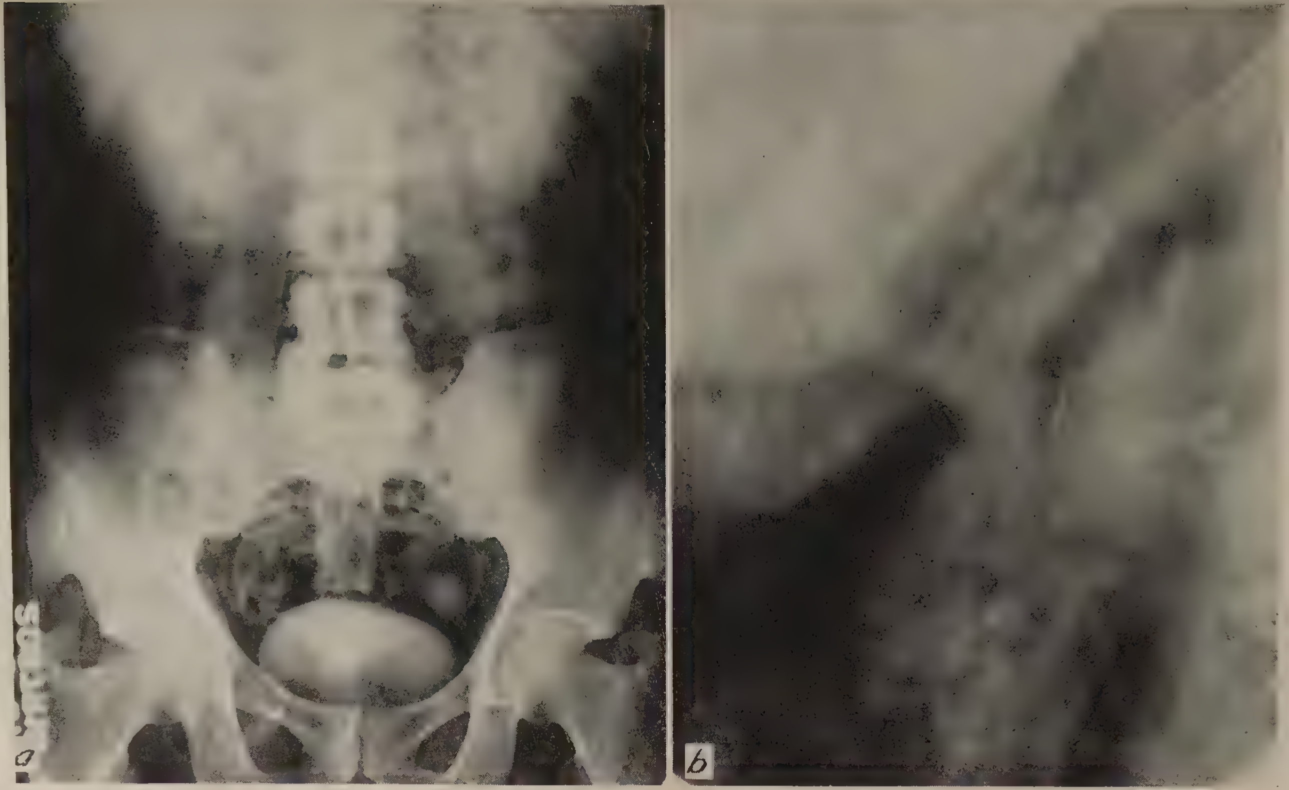
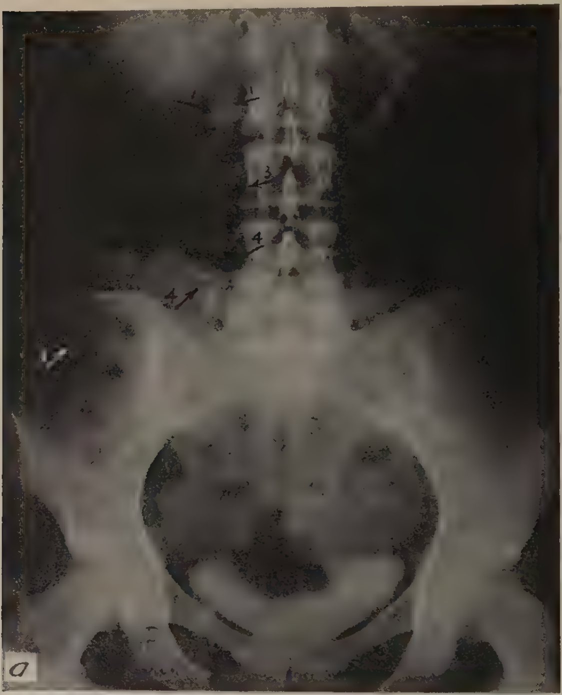


Figure 3. Case 3, E.M., March 28, 1957. (*a*) Film made at 10 min., showing urinary tract adequately visualized. (*b*) Film made at 60 min., showing uniform dilatation of the hepatic and common bile ducts consistent with fibrosis of the sphincter of Oddi. Average diameter of the ducts is 1.0 to 1.2 cm. There are no demonstrable calculi and no evidence of a cystic duct stump. At operation, fibrosis of the sphincter of Oddi was noted; a sphincterotomy was performed with complete relief of the patient's symptoms.



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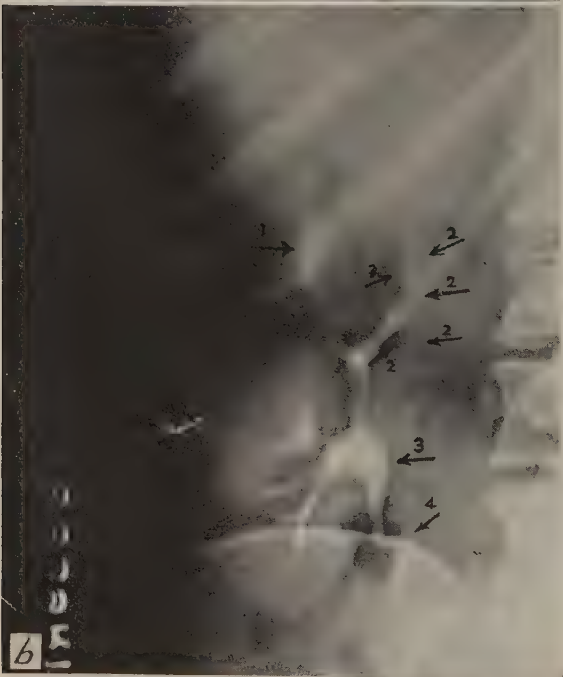

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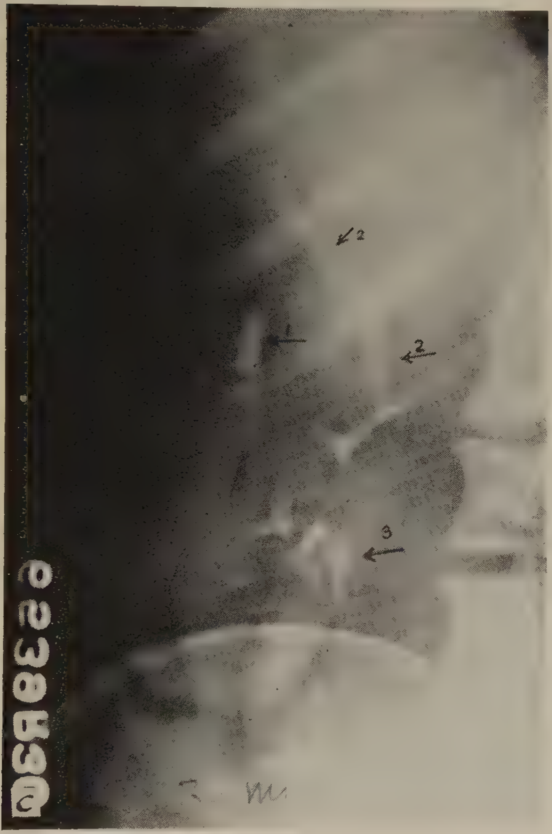

Figure 4. Case 4, S.K., December 12, 1956. (*a*) Upright 10-min. film. Note 1- × 2-cm. calcification at the level of L-2 (arrow 1). Note also low position of the right kidney (arrow 3) with angulation of the upper right ureter (arrow 4). (*b* and *c*) Film made at 15 and 30 min. after injection, showing normal hepatic and common bile ducts (arrow 2). There was no visualization of the gall bladder through a 2-hour period of observation. The calcification is outside the biliary tract. Cause of pain was considered to be a low movable kidney with angulation of upper right ureter, chronic cholecystitis and cholelithiasis, or a calcified node to the right of the lumbar spine. At operation, a chronically inflamed gall bladder filled with nonopaque calculi was removed.

The urinary-tract examination is conducted in the usual manner with films made at 5, 10, and 15 min., including an upright film at 10 min. and a post-evacuation film of the bladder at 15 min. after injection of Duografin. Delayed films of the urinary tract, if indicated, can be obtained readily while the biliary-tract examination is still in progress.

The biliary tract is also examined in the usual manner, with films of the bile ducts made at 10-min. intervals for as long as 1 hour. The patient lies on his back with the left side elevated approximately 15°. This prevents the possibility of overlapping of the shadows of the ducts and the shadow of the spine. If the gall bladder is still present, the patient should be further observed for as long as 2 hours. If the gall bladder is visualized, the examination is concluded in the usual manner. If the gall bladder is absent or fails to visualize, the examination is terminated if and when the bile ducts are adequately visualized.

Careful rotation of the patient will obviate any overlap between the bile ducts and right urinary tract. The initial early renal excretion with visualization of the urinary tract occurs within the first 10 to 15 min. before the bile ducts are adequately visualized. Subsequently, with the patient supine and the left side elevated 15°, the bile ducts are separated from the right urinary tract, neither obscuring the other.

Duografin is supplied in 50-cc. ampules, which is adequate for one dose. This should be warmed to body temperature for greater ease of injection.

Side Reactions

It is gratifying to find that the side reactions with Duografin are fewer than the combined total for Renografin and Cholografin Methylglucamine. At all times, however, there should always be available in the same room where the examination is being conducted an oxygen tank and an emergency tray bearing a number of sterile syringes and needles, 5 per cent sterile glucose solution, Chlor-Trimeton or Benadryl, and Levophed or ephedrine. The person giving the injection should remain with the patient for at least 30 min. and should be within easy reach until completion of the examination.

The incidence and intensity of side reactions can be decreased appreciably by slow injection; the reverse holds true. Pretesting of the patient for sensitivity can be most misleading. Neither the ocular, the intradermal, nor the intravenous tests are reliable, and the ocular may result in local reactions harmful to the eye. Many patients who responded with a positive reaction to the preliminary sensitivity test failed to show any reaction when the total dose was injected, while other patients, with a negative response to the sensitivity test, have had reactions to the dose of varying intensity.

The blood pressure should be determined and recorded before and at frequent intervals during the examination.

Advantages and Disadvantages

Visualization of two systems with one injection at one time is the chief advantage. The patient is prepared once only and only one visit to the department becomes necessary. This is especially valuable when the patient is very sick or if he is an outpatient who lives at a great distance, as he is thus spared the physical as well as the emotional strain of coming for more than one examination. Furthermore, in a busy department, such a procedure results in great saving of time and effort on the part of all concerned—one visit, one entry in the records, one gown, one dressing room, one machine, one technician.

The disadvantage is that the examination tends to be time-consuming, although the time required is less than the total for separately conducted intravenous urography and cholangiography. Adequate provision should be made for ample space and technical assistance if this examination is to be conducted routinely without interfering with the over-all activities and functions of the radiology department.

Material Studied

The material studied includes the results of tests with two hundred patients who were examined with Duografin in our Department of Radiology during the past two years. These patients were referred to us primarily for investigation of the biliary tract and the urinary tract because of indefinite complaints concerning the upper abdomen or the upper right side, anteriorly or posteriorly; because of pain in the right flank and abdomen; or for general check up. While the examination often confirmed the clinical impression or diagnosis, the findings listed in TABLE 1 are especially significant, for they were not suspected or looked for on the basis of clinical history and general physical examination. For the most part, their discovery offered a satisfactory explanation of the patients' symptoms. Correct and effective treatment accordingly was instituted.

Illustrative Cases

Case 1, S. P., a 34-year-old male, was admitted with the chief complaint of intermittent pain in the right upper abdominal quadrant and right loin. After injection of 50 cc. of Duografin, the urinary and biliary tracts were simultaneously and promptly visualized (FIGURE 1).

Case 2, W. P., a 54-year-old male, was admitted with clinical diagnosis of suspected right renal colic or pancreatitis. Cholecystectomy had been performed 20 years previously. The injection of 40 cc. Duografin resulted in prompt and adequate simultaneous urography and cholangiography (FIGURE 2).

Case 3, E. M., a 49-year-old male, was admitted with the chief complaint of epigastric and right upper quadrant pain radiating to the back. Cholecystectomy had been performed 10 years before. After the injection of 40 cc. of Duografin, prompt renal and hepatic excretion occurred (FIGURE 3).

Case 4, S. K., a 42-year-old female, was admitted with a complaint of recurrent right upper quadrant pain. Clinical diagnosis of cholecystitis was made on admission. After injection of 40 cc. of Duografin, the urinary tract and the bile ducts were well visualized (FIGURE 4).

Summary and Conclusion

A safe and reliable procedure is now available for the simultaneous roentgen visualization of the biliary and urinary tracts. It is of greatest value when used in carefully selected cases. Its routine use depends upon the availability of time, space, and personnel in the departments concerned.

ROSE BENGAL AND IODOPYRACET AS RADIODIAGNOSTIC AGENTS IN LIVER AND KIDNEY DISEASES*

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Introduction

During the past 4 years 2 new radiodiagnostic tracer tests have been developed as aids in the diagnosis and management of patients with diseases of the liver and kidneys.[1-8] Both tests are performed externally with the same type of radiation detection equipment that is used for determining radioiodine uptake by the thyroid gland. The rates of organ uptake, excretion, translocation, and blood clearance are measured simultaneously following intravenous injection of minute doses of I^{131}-labeled rose bengal or iodopyracet (Diodrast). The data obtained permit evaluation of vascular, parenchyma, and obstructive disorders of these organs and their excretory passages.

This article is presented (1) to demonstrate the advantages of these simple tracer techniques over multiple biochemical liver tests[9, 10] and complicated urological diagnostic procedures for determining individual kidney function;[11-16] and (2) to describe recent laboratory and clinical studies that have led to improvement in both techniques.

Materials

The I^{131}-labeled rose bengal, Urokon, Diodrast, Hypaque, and colloidal gold supplies are available commercially as sterile solutions having relatively high specific activity. These concentrated solutions may be diluted with sterile water or physiological saline to prepare individual test doses of the desired strength. Dilutions to 1:500 do not alter the blood clearance or organ extraction-excretion rates.

Equipment

The arrangements of the gamma-ray scintillation counting and recording equipment as used for performing the rose bengal hepatogram and the radioisotope renogram tests in rabbits and man are shown in FIGURE 1. Reports have been published that describe these tracer techniques and their precautions and interpretations in detail.[3, 5, 6]

Results with Rose Bengal I^{131}

The normal hepatogram after intravenous injection of a 10-μc. dose of rose bengal (30,000 cpm) is shown in FIGURE 2. The initial liver uptake measurement made 30 to 90 sec. after injection and prior to dye extraction by the liver

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* The investigations reported here were supported by Contract AT(04-1)-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

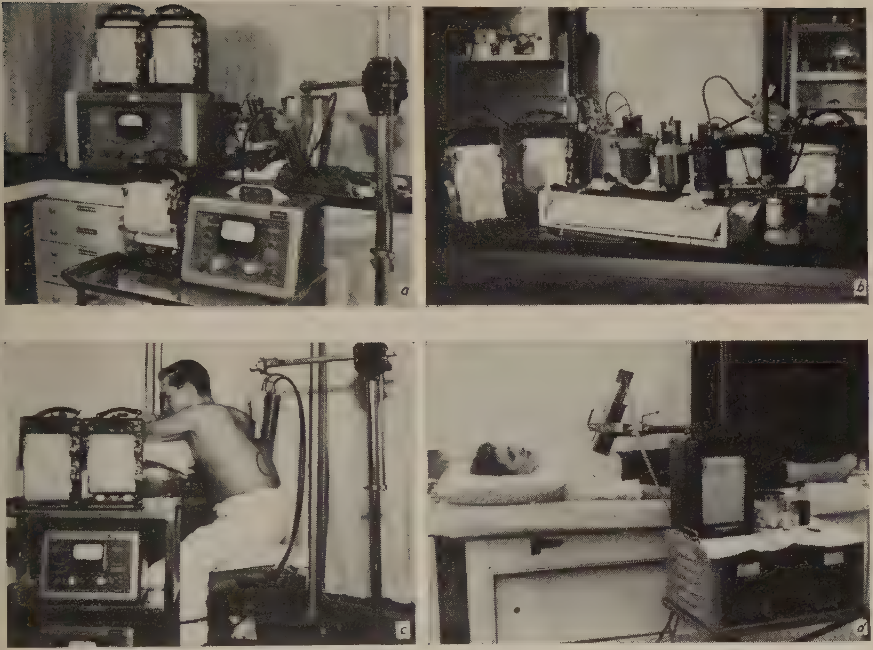
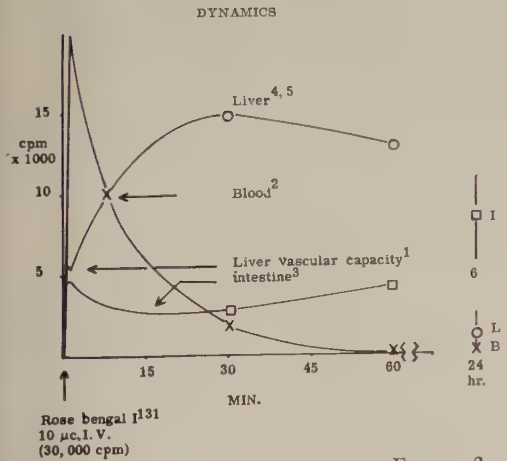


FIGURE 1 (*a*, *b*, *c*, *d*).



NORMAL VALUES

1. Liver vascular capacity (LVC) = $15^{\pm 3}$% of injected dose
2. Blood T/2 = $8^{\pm 2}$ min.
3. Intestinal entry = $15^{\pm 5}$ min.
4. Liver maximum time = $30^{\pm 7}$ min.
5. Liver excretion T/2 = $150^{\pm 30}$ min.
6. Retention (24 hr.)
   - liver <50% of LVC
   - blood 0
   - intestine >100% of LVC

FIGURE 2

cells gives an index of liver vascular capacity (LVC). This measurement has been demonstrated to be reliable, ±10 per cent, by making a similar measurement after the injection of an equal dose of radioiodinated serum albumin.[2] With the equipment used, the liver vascular capacity is about 15 per cent of the injected dose. The rates of dye clearance from the blood and the extraction by the liver have a reciprocal relation with a half-time of about 8 min. The dye enters the small intestine after approximately 15 min. and subsequently at rates similar to its rate of excretion from the liver, which has a half-time of approximately 150 min. Maximum liver uptake is reached in normal subjects in about 30 min. Twenty-four-hour dye retention in the liver is less than 50 per cent of the value for liver vascular capacity; it is greater than 100 per cent of this value in the intestine, and the blood is completely cleared. Less than 2 per cent of the dose is excreted in the urine or accumulated in the thyroid in 24 hours.

The Hepatogram in Primary Liver Disease

Hepatogram findings from 71 patients with primary liver diseases compared with those from 60 patients with normal liver functions are summarized in TABLE 1. Cirrhotic patients usually have a reduction in liver vascular capacity and abnormally slow blood clearance and liver excretion rates, but intestinal entry time is usually within normal limits of 15 ± 5 min. The hepatograms from patients with acute and chronic hepatitis are similar except that LVC values are normal or only slightly reduced. In patients with cardiac hepatomegaly the hepatogram may vary from normal to those seen in patients with advanced cirrhosis; however, LVC values are usually normal or somewhat elevated. Finally, the test is useful in studying patients with ascites of unknown origin; cirrhosis is readily detected, and normal findings are strong evidence against primary liver disease.

Case Report 1: portal cirrhosis. Results of repeated hepatograms together with multiple biochemical liver tests determined in a patient with advanced but stabilized portal cirrhosis are shown in FIGURE 3. The data demonstrate: (1) the reproducibility of the hepatograms performed 2 months apart; (2) the equal sensitivity of the rose bengal blood clearance half-times of 42 and 45 min. with the 45-min. Bromsulphalein (BSP) blood retention of 50 per cent; and (3) the greater sensitivity of the hepatogram over the cephalin flocculation

TABLE 1

TRACER HEPATOGRAM FINDINGS IN PRIMARY LIVER DISEASES

(Comparison with Normal Values)

	No. of tests	Liver vascular capacity (percentage injected dose)	Blood clearance half-time (min.)	Intestinal appearance time (min.)	Liver excretion half-time (min.)	Liver retention at 24 hr. (percentage LVC)
Normal liver functions	60	12 to 18	6 to 10	10 to 25	150 ± 50	15 to 30
Portal cirrhosis	40	5 to 15	6 to 100	10 to 25	150 to >600	30 to 100
Acute and chronic hepatitis	15	10 to 15	6 to >60	10 to 25	150 to >300	30 to 100
Cardiac hepatomegaly	6	15 to 20	6 to >30	10 to 25	150 to >300	15 to 100
Ascites (cause unknown)	10	5 to 18	6 to >60	10 to 25	150 to >300	15 to 100

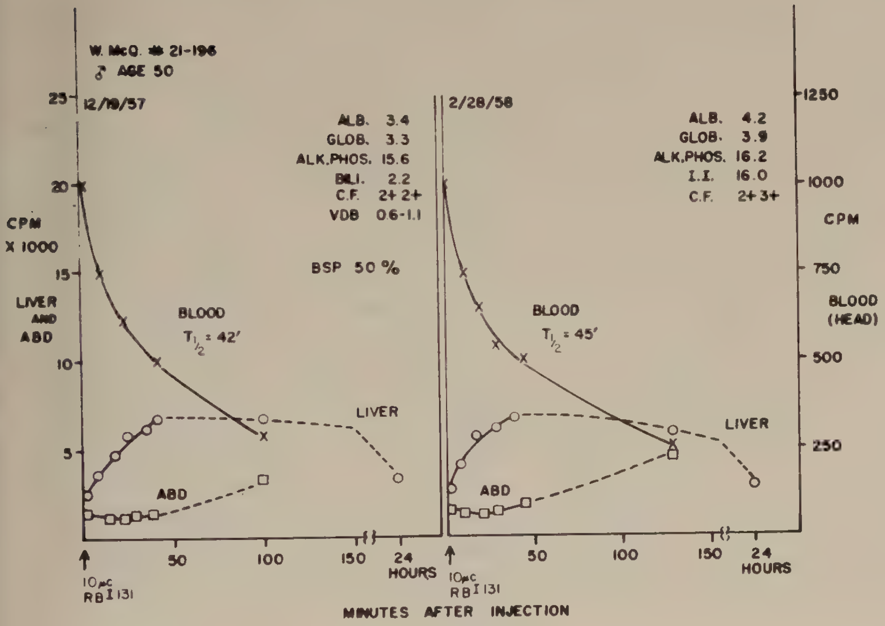


FIGURE 3

test in cirrhosis. Most important, the hepatogram also indicates the marked reduction in the LVC, which is a most important aspect of the pathology of cirrhosis. Furthermore, the increasing level of radioactivity in the intestine demonstrates the absence of biliary obstruction, whereas a simple liver uptake excretion curve could be interpreted as indicating obstructive disease.

Case Report 2: acute severe infectious hepatitis. The results of repeated hepatograms and biochemical tests in a patient having severe acute infectious hepatitis are shown in FIGURE 4. The hepatogram results mirrored the clinical picture more closely than the biochemical tests, particularly the cephalin flocculation, which remained the same in spite of a sharp fall in bilirubin and thymol turbidity. The elevated alkaline phosphatase at the height of the disease and its low level subsequently may have reflected a transitory period of partial intrahepatic obstruction. The low value of rose bengal liver retention at 48 hours in the first test gave positive proof against a significant degree of biliary obstruction. The subsequent clinical course and repeated liver tests confirmed the original diagnosis.

The Hepatogram in Obstructive Liver Diseases

Data in TABLE 2 summarize the hepatogram findings in 95 patients with obstructive liver diseases compared with subjects having normal liver functions. The hepatograms indicate obstruction by delayed intestinal entry time (greater than 30 min.) of dye, by increased time to reach maximum liver uptake (greater than 50 min.), and by abnormally high liver retention of dye at 24 hours (greater than 50 per cent of LVC).

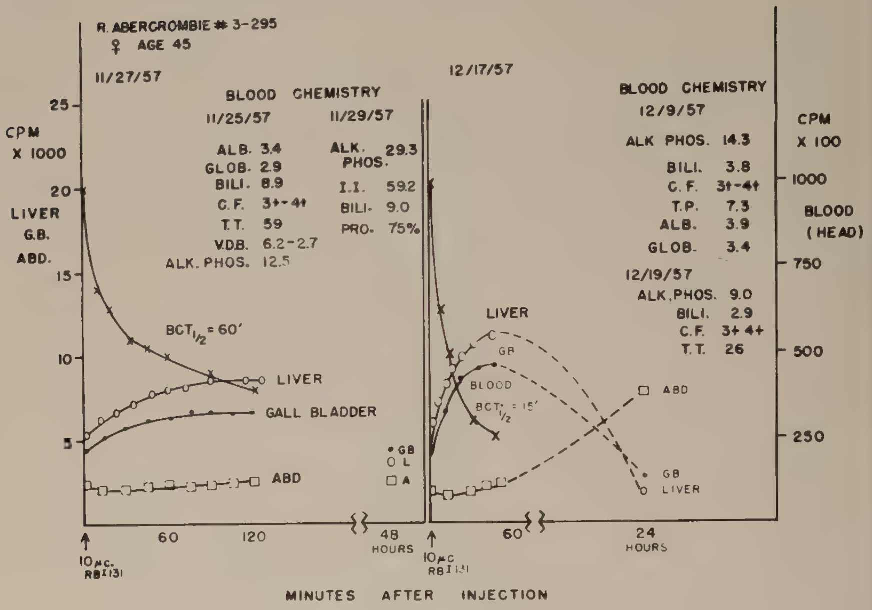


FIGURE 4

Intermittent biliary obstruction is readily detected by repeated tracer tests that indicate changes in bile flow interference immediately, whereas days or weeks are required for indirect biochemical liver tests to give the same information.

In our experience there have been only 3 cases in which serial tracer tests did not reveal some differential diagnostic information. These were patients who had severe jaundice of several weeks' duration, and who were first tested only after liver function had deteriorated to the point where the liver cells

TABLE 2
THE HEPATOGRAM IN OBSTRUCTIVE LIVER DISEASE
(Diagnostic Features)

	No. of tests	Intestinal entry time (min.)	Time for maximum liver uptake (min.)	Liver retention at 24 hr. (percentage LVC)
Acute severe biliary tract obstruction	10	>50	>50	100 to 300
Partial biliary tract obstruction	60	>30	>50	30 to 150
Intermittent biliary tract obstruction	15	>30	normal or prolonged	20 to 150
Chronic severe biliary tract obstruction	10	>30	>100	>100
Subjects with normal functions	60	15 ± 5	30 ± 7	<30

were unable to extract the dye from the blood or the dye was regurgitated with the bile into the circulation. Such a state may develop after prolonged extra- or intrahepatic biliary obstruction, as well as during the course of severe primary liver disease. Under such circumstances liver biopsy and surgical exploration are hazardous procedures, and the physician must rely heavily on clinical experience because other laboratory findings may also fail to provide adequate diagnostic data.[9]

The diagnostic value of the hepatogram is best demonstrated from records of patients in whom the final diagnoses have been established by biopsy, surgical exploration, or both. These examples show the reproducibility of the hepatogram (as well as its diagnostic reliability) in comparison with results of standard liver tests and with pre- and postoperative clinical and pathological findings.

Case Report 3: complete biliary obstruction. Data from a patient with nearly complete biliary obstruction of 3 weeks' duration caused by a stone in the common bile duct are shown in FIGURE 5. The pre- and postoperative hepatogram findings reflected accurately and quickly the surgical correction of biliary obstruction. The alkaline phosphatase values lagged behind the hepatogram in reflecting release of obstruction. The relatively slow recovery of liver function in this patient with jaundice of relatively long duration was demonstrated by the hepatograms, which also paralleled the clinical course. The less sensitive biochemical tests indicated relatively little secondary liver injury.

Case Report 4: intermittent biliary obstruction. An example of intermittent biliary obstruction demonstrated by repeated pre- and postoperative hepatograms is presented in FIGURE 6 with the pre- and postoperative biochemical

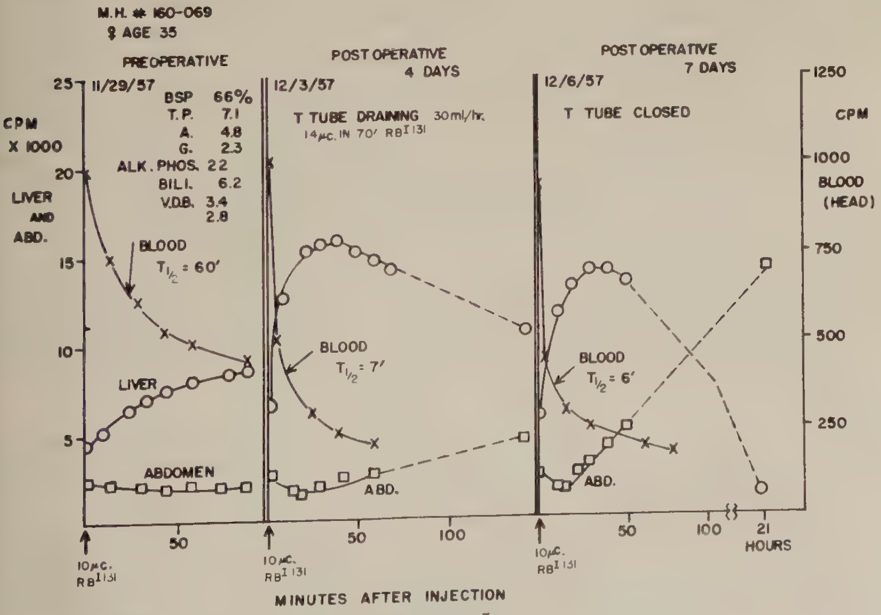


FIGURE 5

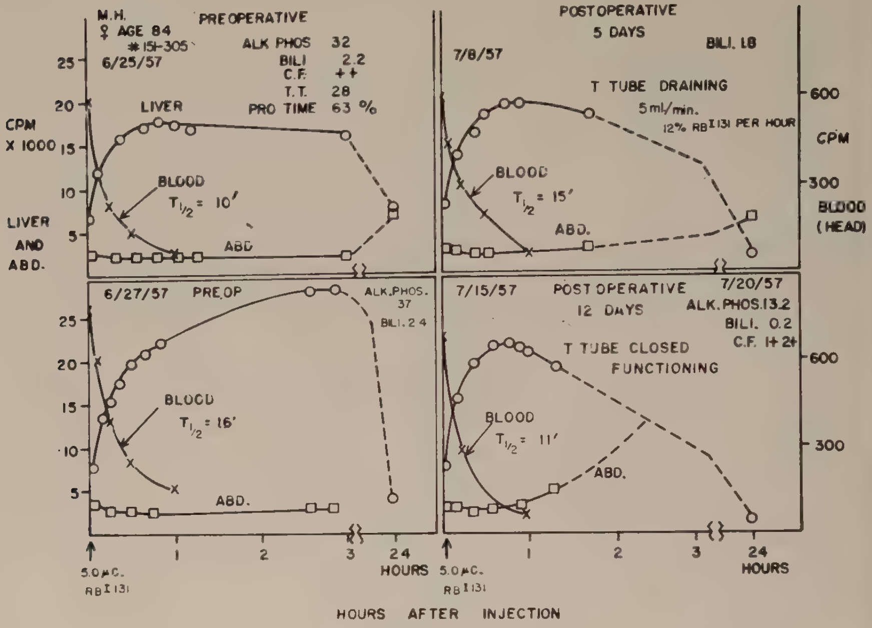


FIGURE 6

liver test results. The hepatogram findings reflected the underlying physiological disturbances more accurately than the biochemical tests. The obstruction was incomplete and transient and, accordingly, there was relatively little associated parenchymal liver damage. Recovery took place promptly, as demonstrated by postoperative hepatograms.

Case Report 5: transient biliary obstruction. Data presented in FIGURE 7 were obtained from a young woman with a recurrent attack of jaundice that occurred 3 months after cholecystectomy and common bile duct exploration. A clinical diagnosis was difficult because several transfusions had been made during the recent operation. The first hepatogram, performed shortly after her second admission, showed partial biliary obstruction and moderate secondary liver damage. These findings compared well with the biochemical liver tests. The second hepatogram, performed 4 days later, after the acute episode of pain, chills, fever, and jaundice had subsided, showed that her partial biliary obstruction had been released spontaneously; these findings correlated with the clinical picture.

However, biochemical evidence for obstruction (alkaline phosphatase) increased during this period and did not reflect the true condition of biliary tract patency until 2 weeks later. Clinical and laboratory findings in this patient are most consistent with a diagnosis of transient obstructive jaundice resulting from a recurrent common-duct stone that was passed spontaneously. Although surgical intervention was seriously considered during the first few days of the patient's second hospitalization, the hepatogram findings provided the necessary assurance to continue with medical management.

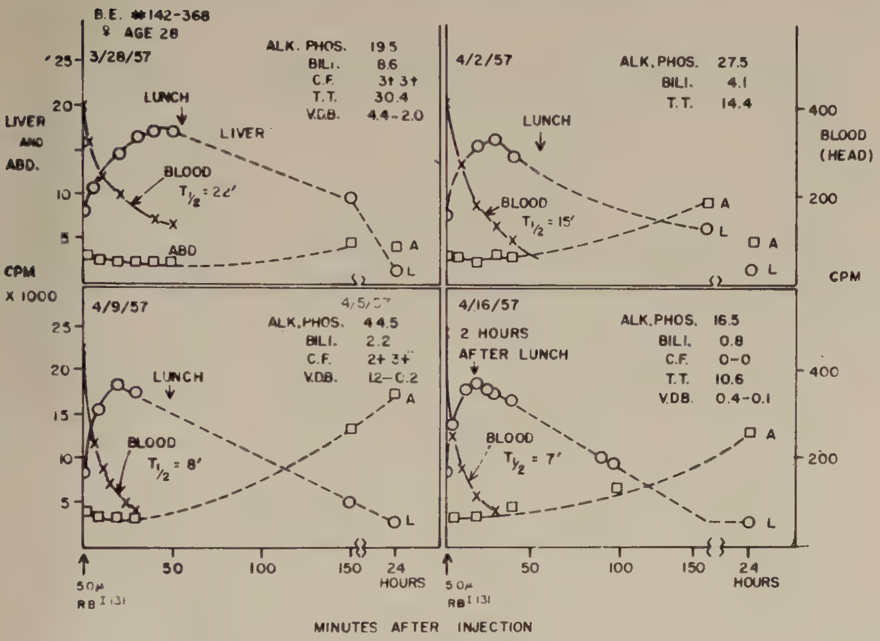


FIGURE 7

Case Report 6: severe chlorpromazine jaundice. Comparison between repeated hepatograms and biochemical liver test results performed in a patient with an unusually protracted and severe case of obstructive jaundice due to chlorpromazine are presented in FIGURE 8. Liver biopsy showed cholangiolar bile stasis, normal triads, and no dilation of the intrahepatic bile ducts. Laboratory findings by hepatograms obtained before and after a course of cortisone and tetracycline therapy showed slight improvement in liver function and bile flow interference; biochemical test results showed insignificant changes. Clinically there was definite improvement in bowel function, but little change in the jaundice. The hepatogram findings provided evidence that the obstruction was incomplete initially and diminished during medical management. Again surgical intervention had been considered, but the hepatograms gave the necessary assurance to continue with medical treatment.

Recent Developments with Rose Bengal

Rose bengal-BSP stress tests. It is well known that most biochemical liver tests are relatively insensitive and nonspecific.[10] Therefore, efforts have been made to increase the sensitivity of the rose bengal tracer test by placing the polygonal cells under stress with various physiological loading agents; these have included Bromsulphalein (BSP), glucose, glycine, and other amino acids. BSP has been shown to be an effective stress-producing agent. The dye is extracted from the blood by polygonal cells of the liver much as rose bengal is extracted.[17, 18] When both dyes are injected simultaneously as a mixture

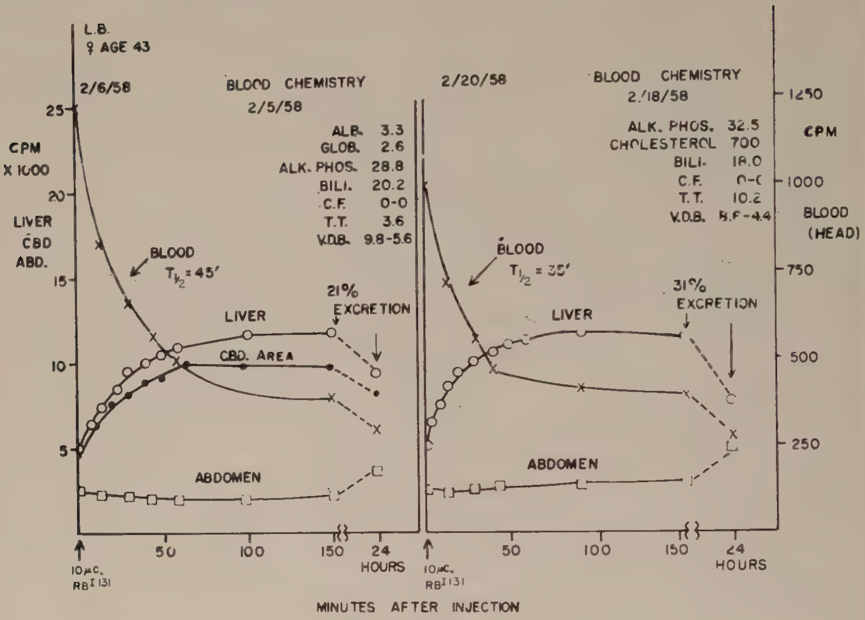


FIGURE 8

containing microgram amounts of rose bengal and 3- to 5-mg./kg. doses of BSP, the normal liver is able to extract both agents at nearly the same rates as either agent separately. However, in patients with asymptomatic liver disease and in animals with minimal liver damage from CCl_4 poisoning, blood clearance of rose bengal in the mixture is much slower than that of a tracer dose administered separately.

Pathophysiological correlations: acute CCl_4 poisoning. Data presented in TABLE 3 show the correlation between rose bengal-BSP blood clearance rates

TABLE 3
STRESS TEST–BLOOD CLEARANCE VALUES AND LIVER PATHOLOGY IN RABBITS DURING DEVELOPMENT OF AND RECOVERY FROM ACUTE CCl_4 POISONING*

Time after poisoning	No. of animals	Blood clearance half-time, min. (average values)	Pathological classification
Controls	106	3.6	1
6 hr.	6	7.4	2
18 hr.	6	7.7	3
24 hr.	13	15.3	4
72 hr.	9	14.0	3
7 to 8 days	15	6.3	2
13 to 14 days	7	4.0	1
20 to 21 days	8	3.7	1
27 to 28 days	6	3.7	1

* All animals were poisoned with CCl_4 in olive oil (50 mg./kg.) by gastric intubation. The stress test consisted of an I.V. injection of rose bengal I^{131} (6.0 µc./kg.) + BSP (5 mg./kg.).

TABLE 4

TRACER- VERSUS STRESS-TEST RESULTS WITH ROSE BENGAL I^{131} AND BSP IN RABBITS POISONED WITH CCl_4 ONCE A WEEK*

Animal	Control values	Days after onset of poisoning							
		7	14	21	28	35	42	49	56
					Blood clearance half-times, min.				
L-7	2.0	3.0	3.5	3.0	3.5	*7.5*	Dead	—	—
M-8	3.0	3.0	4.5	6.5	5.0	*9.5*	3.0	*7.0*	6.0
R-9	1.5	3.0	3.0	2.0	5.0	*7.0*	5.0	*3.5*	3.0
S-10	2.5	4.0	3.5	3.0	3.0	*9.5*	7.5	*11.0*	11.0
T-11	3.0	2.0	3.0	4.0	3.5	*10.0*	4.0	*10.0*	6.0
U-12	2.0	2.0	2.0	2.5	4.0	*4.0*	4.0	*8.0*	5.0
Av. values	2.3	2.8	3.2	3.5	4.0	*7.9*	4.7	*7.9*	6.2
					Minutes to maximum liver uptake				
L-7	7.0	8.0	8.0	8.5	5.5	*15.5*	Dead	—	—
M-8	5.5	11.0	8.5	11.0	7.0	*14.0*	8.5	*13.5*	11.0
R-9	9.0	6.5	7.0	6.5	6.5	*9.5*	14.5	*8.5*	8.0
S-10	7.5	7.0	9.5	9.0	8.0	*11.5*	9.5	*19.5*	10.0
T-11	7.5	8.0	8.0	8.5	7.5	*8.0*	7.5	*10.0*	8.0
U-12	6.0	8.0	7.5	6.0	6.5	*5.5*	10.0	*7.0*	7.5
Av. values	7.1	8.0	8.0	8.2	6.6	*10.6*	10.0	*11.7*	8.9

* Rose bengal I^{131} tracer and stress tests performed 7 days after poisoning. Values for stress tests are italicized.

and liver pathology in a large group of animals during the development and recovery from acute CCl_4 poisoning (50 mg./kg.). The findings indicate that physiological disorders and histological changes develop within 6 hours and reach a maximum during the next 24 to 72 hours. Considerable recovery occurs by 7 to 8 days and is nearly always complete by 14 days. Separate tracer-test results in the same animals are entirely negative by 9 to 10 days. However, during this same period and for a few days prior to it, the stress-test findings are more positive in most instances than tracer-test results. After recovery has occurred (14 to 28 days) results of both types of tests are negative. This pathophysiological correlation demonstrates the reliability of the rose bengal tests in reflecting the degree of liver injury and the ability of the BSP-rose bengal stress test to detect minimal liver injury in rabbits.

Studies in rabbits during chronic CCl_4 poisoning. Data presented in TABLE 4 demonstrate that there is a progressive impairment of liver function in rabbits poisoned once a week with CCl_4 administered at a dose level of 10 mg./kg. The average values of blood clearance half-time and time-to-maximum liver uptake increased gradually. After 28 days, stress tests are more positive than those for tracer procedures in most instances. The blood clearance half-time appears to be a more sensitive index of liver damage than the time to reach maximum liver uptake. Histological examinations reveal development of pathological changes characteristic of early cirrhosis.

Tracer versus stress-test studies in patients. Tracer and stress-test hepato-

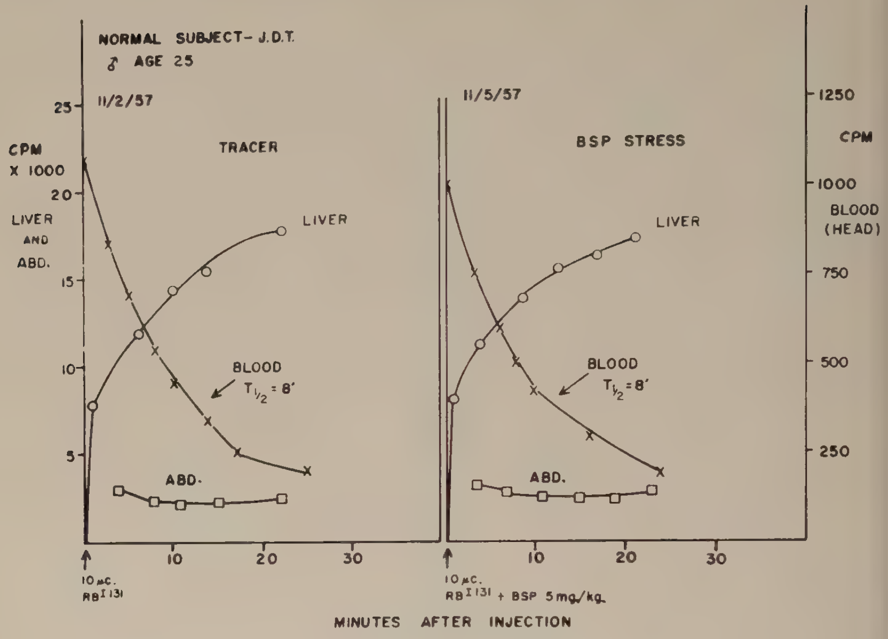


FIGURE 9

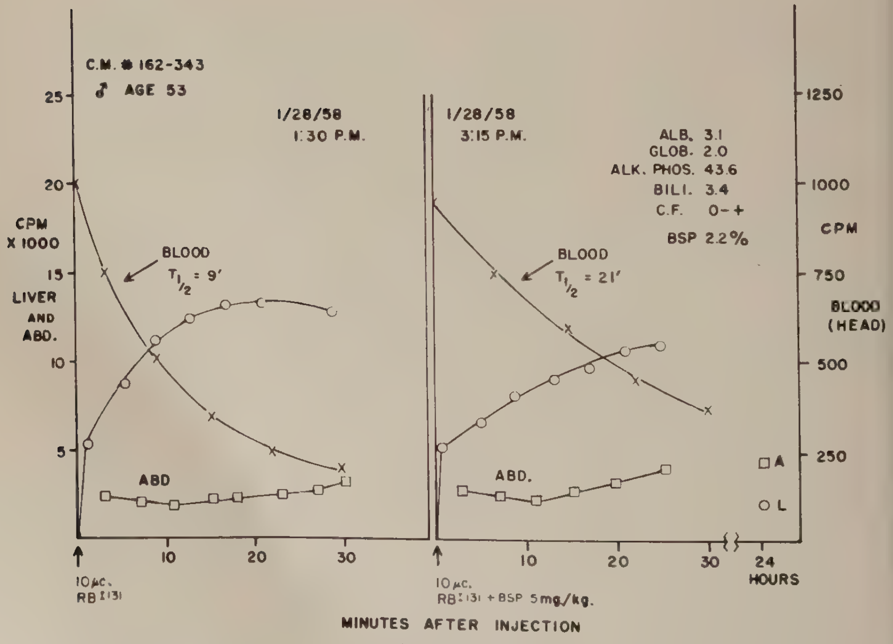


FIGURE 10

TABLE 5

ROSE BENGAL TRACER TESTS VERSUS BSP-ROSE BENGAL BLOOD CLEARANCE STRESS TESTS* IN PATIENTS

No. of cases	Type of patient	Blood clearance half-time tracer dose (min.)	Blood clearance half-time BSP stress test (min.)
10	With normal liver functions	8 ± 2	10 ± 2
20	With minimal liver disease	10 ± 2	20 ± 5

* BSP stress test consists of simultaneous injection of 3 to 5 mg./kg. of Bromsulphalein (BSP) with the tracer dose (1 to 10 μg./kg.) of rose bengal.

gram findings from a normal subject presented in FIGURE 9 show that there is little difference between the blood-clearance or liver-uptake rates whereas, in a 53-year-old chronic alcoholic with relatively normal biochemical findings, the stress hepatogram (FIGURE 10) is distinctly positive and the tracer-test results are within the upper limits of normal. Tabulated data from 10 normal subjects compared with 20 patients having known or suspected liver disease are presented in TABLE 5. Patients having histories of chronic alcoholism and persistent liver enlargement from previous hepatitis frequently show strongly positive stress-test results.

Tracer Studies on Liver Blood Supply

Patients with advanced portal cirrhosis have a 30 to 70 per cent reduction of blood flow compared with normal values (1500 ml./min.).[10, 18-20] These findings correlate well with the simple external measurement of liver vascular capacity made with rose bengal I^{131}. However, both of these procedures fail to measure functional impairment of the portal circulation of the liver separately from its arterial supply. It is known that in cirrhosis the arterial circulation predominates and that progressive portal hypertension develops.[10] Because of the latter condition and other factors, hemorrhage from esophageal varices becomes one of the most serious complications of this disease. Portal hypertension can be corrected by various surgical procedures that bypass the liver and provide portal decompression.[21] Most patients do not receive the benefit of prophylactic surgery for several reasons, one of which is lack of a simple functional test for the detection and evaluation of such vascular defects early in the course of the disease. Therefore, experiments were conducted to develop a tracer technique to measure impairment of portal blood supply and to evaluate the relative importance of the portal venous versus arterial circulation of the liver.

Relative importance of portal versus arterial blood supply. The capacity of the liver to extract rose bengal I^{131} is reduced three to five times immediately after portal vein ligation in rabbits, but is hardly altered by tying the hepatic artery. Furthermore, acute portal vein and hepatic artery ligation have different effects on bile excretion rates and on bile flow response to a hydrocholeretic agent in rabbits. Data in TABLE 6 show that a rabbit with its hepatic artery tied continues to form bile at a normal rate and responds to injection of sodium dehydrocholate with a sharp increase in bile volume whereas, in an animal

TABLE 6

EFFECTS IN RABBITS OF PORTAL-VEIN AND HEPATIC-ARTERY LIGATION ON BILE SECRETION AND RESPONSE TO DECHOLIN

Volume of bile secreted in 15-min. periods (ml.)*			
Experiment 1			
Response to portal-vein ligation		Response to sodium dehydrocholate	
A. Vein intact	1.95	A. Vein intact	4.3
B. Vein tied	0.75	B. Vein tied	0.45
Experiment 2			
Response to hepatic-artery ligation		Response to sodium dehydrocholate	
A. Artery intact	1.5	A. Artery intact	4.2
B. Artery tied	1.5	B. Artery tied	3.6

* Bile samples collected by cannulation of the common bile duct.

with its portal vein ligated, there is a reduced flow and an inability to respond to the same agent. These findings demonstrate the importance of the portal supply in rabbits.

Dual blood clearance tests for impaired portal function. Progressive impairment of the portal circulation occurs during the production of experimental cirrhosis in rabbits. This obstructive vascular defect manifests itself by gross differences in the rates of rose bengal blood clearance measured over portal (abdominal) versus nonportal (head) areas. These defects were observed in 9 of 12 rabbits chronically poisoned with CCl_4 for 10 weeks; in these animals tracer studies were repeated at weekly intervals. The findings (FIGURE 11) from a typical rabbit demonstrate the manifestations of this portal vascular defect. It is apparent that the rose bengal blood clearance rates measured over the abdominal (portal) area decreased much more than the nonportal blood clearance rates measured over the head. As cirrhosis is induced, there is also progressive reduction in LVC to the low levels seen in cirrhotic patients. This dual blood clearance technique is readily adaptable for clinical application.

Liver Blood Flow Studies with Colloidal Gold and Rose Bengal

Preliminary studies have been made with colloidal gold^{198} and rose bengal I^{131} in 50 rabbits to evaluate further the influence of circulatory disorders of the liver on polygonal cell function. The blood clearance and liver extraction rates of intravenously injected colloidal gold in doses less than 30 μg./kg. are not appreciably influenced by gross alteration in function of the polygonal and von Kupffer's cells. The blood clearance rates of rose bengal are retarded markedly by polygonal cell damage, as well as by impairment of the portal circulation.

Ligation of the portal vein causes a three- to eightfold reduction in the rates of blood clearance and liver extraction of colloidal gold and a three- to fivefold reduction with rose bengal. In normal rabbits, tracer doses of colloidal gold

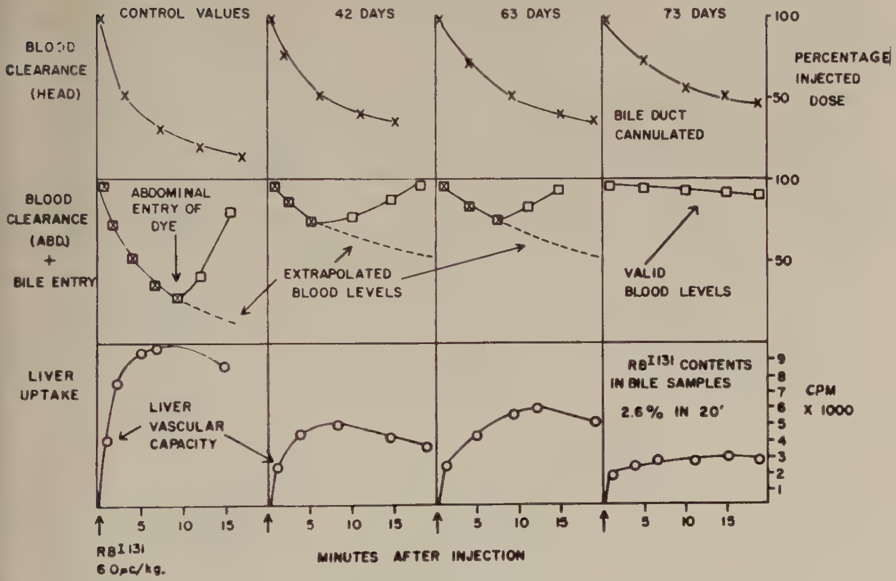

DEVELOPMENT OF PORTAL VASCULAR FUNCTIONAL IMPAIRMENT AND CIRRHOSIS

FIGURE 11

and rose bengal are cleared from the blood with half-times of about 30 sec. and 2.5 min., respectively. In animals having moderately severe liver damage from acute CCl_4 poisoning (75 μg./kg.) the rose bengal blood clearance and liver extraction rates are consistently decreased to half-times of 5 to 15 min. The same animals are still capable of handling colloidal gold at normal or near normal rates. Thus it appears that in rabbits this agent has its primary effect on the polygonal cells rather than on the vascular bed during the acute phase of the poisoning. However, with animals suffering from subacute (8 to 10 weeks) CCl_4 poisoning, there appears to be a relatively greater vascular impairment.

Further work is necessary before more exact estimates may be made with colloidal gold in respect to impairment of the hepatic circulation. It is essential that the particle size distribution and concentration of the test material be kept within narrow limits. These two parameters have not been established with sufficient accuracy at present either in animal studies or clinical investigations. It appears that valuable data may be obtained with this agent in the future, especially in evaluating the vascular components of liver disease—particularly in patients with chronic hepatitis or cirrhosis.

Radioisotope Renogram Results

Typical Diodrast renograms. Typical renograms from patients with common unilateral renal disorders are shown in FIGURE 12. The normal right renogram following intravenous injection of a tracer dose of Diodrast has a curve com-

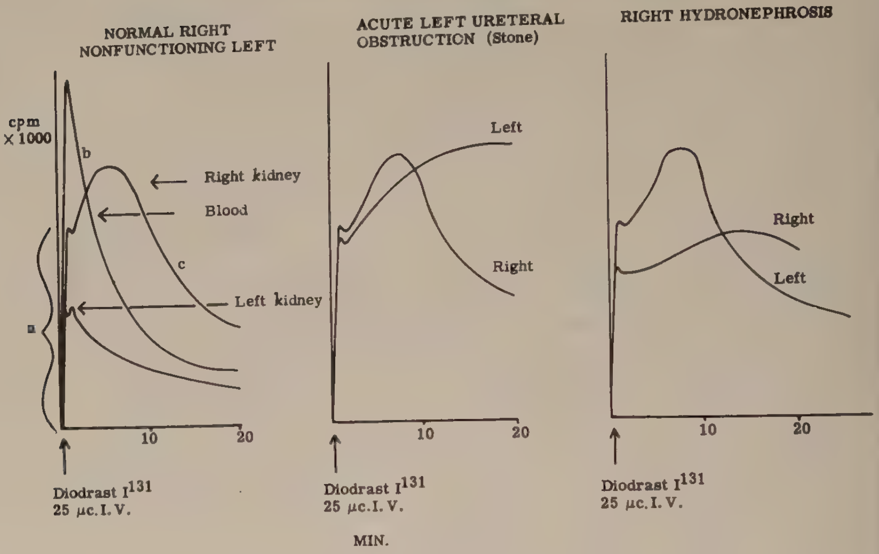


FIGURE 12

posed of 3 distinct segments: the first, a sudden rise in radioactivity, indicates renal vascular capacity; the second, a slower rise, represents active tubular secretion of Diodrast because there is a reciprocal fall in blood radioactivity during the same 3- to 6-min. period; and the third segment, a rapid fall to near-background levels within 15 to 20 min., indicates patency of the upper urinary tract. The renogram from the nonfunctioning left kidney shows a reduced vascular leg and absence of a secretory segment, and the curve tends to parallel that of blood clearance.

The renograms in the center of FIGURE 12 are from a patient with acute obstruction of the left ureter caused by a stone. The diagnostic feature is the prolonged second segment, reproduced in man by inflation of a ureteral bag catheter and, in animals, by ureteral ligation.[6]

The renograms on the right are from a patient with left hydronephrosis from stricture at the ureteral pelvic junction. The abnormal features here are the reduced vascular capacity, the slow and prolonged uptake, and the delayed-excretion segments, which indicate reduced blood supply, impaired tubular function, and partial obstruction in the upper urinary tract.

In 410 patients with normal renograms, only 8 (2 per cent) were subsequently shown by standard methods to have kidney disease. Forty-five patients with a nonfunctioning or absent kidney were tested, and the renogram findings were confirmed in all instances by either intravenous or retrograde pyelograph. Forty-nine patients with hydronephrosis have been tested with renograms and, likewise, confirmed by standard methods.

Neurogenic shock. This condition has been observed twice in patients during performance of the renogram test. In both instances the reaction was most probably induced by repeated venipunctures and not by reaction to the test

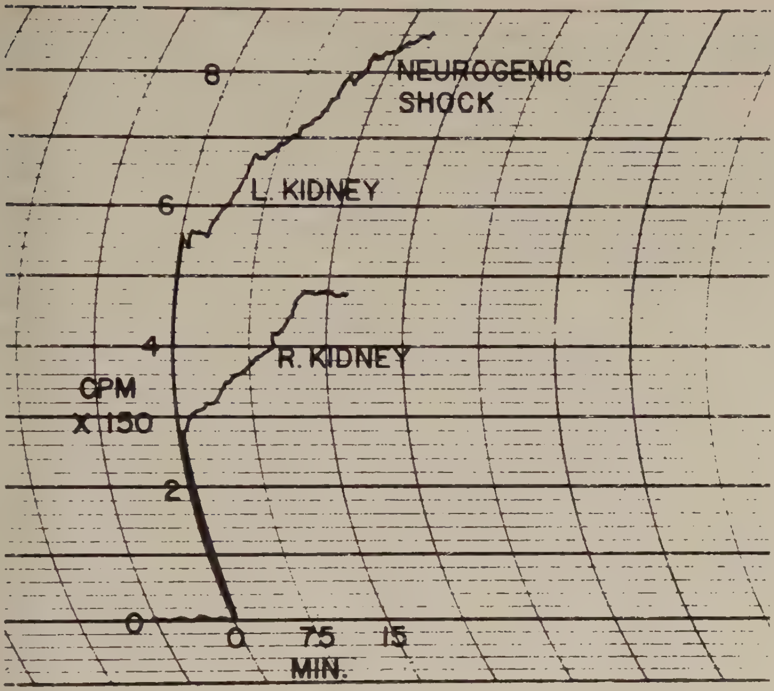


FIGURE 13

agent. The clinical picture in both cases was similar. The patients appeared pale, apprehensive, and complained of feeling faint. Pulse rates were slow and the blood pressure readings fell to low levels. Recovery occurred rapidly and spontaneously. In the first patient[6] the reaction occurred during a tracer test (FIGURE 13) that was made 10 min. after injection of a priming dose of Urokon (25 ml. of a 70 per cent Urokon solution). In the second patient the reaction was less severe and occurred during a tracer test with Diodrast I^{131}. In both instances the renograms showed in both renal areas a continuing accumulation of test material similar to that found in animals and man, with complete bilateral ureteral obstruction. However, in the second patient a rapid fall in renal radioactivity occurred after 20 min., as if there had been a sudden release of ureteral obstruction. At this time the patient's blood pressure increased and her shock symptoms subsided. The 2 most likely explanations for these findings are bilateral ureteral spasm and depression of urine formation, with accumulation of test material in the tubular cells; the latter resulted from reduced blood flow.

Detection of unilateral renal disorders in hypertensive patients. The Diodrast renogram has been used for screening hypertensive patients to detect those with disorders of 1 kidney who may be benefited by nephrectomy or other surgical measures (TABLE 7). The renogram indicated absence of renal disease in all patients with essential hypertension. Thirty patients showed bilaterally ab-

TABLE 7

DIODRAST RENOGRAM RESULTS*

Renogram diagnosis	No. of patients	Final diagnosis (standard individual renal-function tests)	No. of patients
Essential hypertension	23	Essential hypertension	23
Bilateral renal disease†	30	Bilateral renal disease	29
Unilateral renal disease†	22	Unilateral renal disease	21

* Obtained in screening hypertensive patients for renal disease.

† Patients with falsely positive renograms had essential hypertension.

TABLE 8

DIAGNOSES, THERAPY, AND COURSE OF TWENTY-ONE HYPERTENSIVE PATIENTS WITH UNILATERAL RENAL DISEASE

No. of patients	Diagnoses	Therapy		Course following treatment
		Surgical	Medical	
14	Chronic pyelonephritis	Nephrectomy 10	Observation 4	Surgical: 4 cured, 5 improved, 1 died Medical: all 4 unchanged
2	Hydronephrosis	Lithotomy 1	Observation 1	Surgical: cured Medical: unchanged
1	Coarcted renal artery	Resection		Surgical: cured
1	Agenesis with infection	Nephrectomy		Surgical: improved
1	Congenital rotation		Observation	Unchanged
1	Prostatic obstruction	Prostatectomy		Improved
1	Partial renal infarction		Observation	Spontaneous cure

normal renogram tracings and 22 had abnormal renograms unilaterally. By comparison with 1 or more standard tests for individual kidney function the renogram correctly localized the abnormal kidney or absence of renal disease in 73 of 75 patients. The 2 patients with false positive tests had essential hypertension.

Diagnoses, therapy, and course of patients with renal hypertension. TABLE 8 shows the diagnoses, therapy, and course of 21 hypertensive patients with proved unilateral renal diseases. Fourteen patients had chronic pyelonephritis. Nephrectomy was performed in 10, and 4 were observed medically. Of the 10 surgical patients, 4 were cured, 5 improved, and 1 died. Of 2 patients with hydronephrosis, 1 was cured by removal of a ureteral stone. One patient with agenesis of the left kidney was improved considerably after nephrectomy. The most remarkable cure followed resection and repair of a coarcted right renal artery in a 24-year-old woman with severe hypertension of 1 year's duration. Her right renogram showed reduced vascular capacity, decreased cell function, and impaired drainage. The excretory urogram and retrograde pyelogram tests were both normal. The precise diagnosis was made by aortography and confirmed by individual kidney clearance tests. Her postoperative renograms were negative and her blood pressure has remained within normal limits for the past 30 months.

Recent Developments

In the past few months, 50 patients with a variety of renal disorders have been studied with the Miokon I^{131} renogram and new equipment. The latter consists of 2 sets of lead-collimated scintillation detectors with 2½-in. apertures, the 1½-in. crystals withdrawn 2 in. into the shields. Otherwise, the equipment is similar to that used originally except that a third set is employed to register blood clearance, with the detector placed over the side of the head. It has been proved that Miokon and Hypaque are excreted almost completely by the kidneys; less than 1.0 per cent is excreted in the bile of patients recovering from cholecystectomies. The configuration of the Miokon renograms obtained with the new detectors positioned perpendicularly toward each kidney is similar to that of Diodrast renograms, except that the slope of the second segment is somewhat less steep. This technique appears to be an improvement because Miokon and Hypaque are more kidney-specific than Diodrast and exact localization of kidney areas is less critical. During these studies, 8 hypertensive individuals have been demonstrated to have unilateral renal disease by this screening procedure.

Discussion

Liver studies. Although extensive investigations of liver structure and function have been made[10] the present-day physician is frequently puzzled by patients with nonhemolytic jaundice. Individuals having laboratory evidence of biliary obstruction and associated parenchymal liver damage pose some of the most difficult diagnostic problems in medicine.[9] When jaundice is caused by mechanical obstruction of the common bile duct, medical measures are of no avail and delayed surgical treatment diminishes the patients' chances for recovery. When jaundice is due to primary liver damage medical treatment is indicated, whereas surgical intervention is harmful.[9] Most biochemical tests for liver disease and biliary obstruction are insensitive, and few are organ-specific;[10] equivocal findings are frequently obtained when laboratory aid is most needed.[9, 10] It is in such patients that repeated rose bengal hepatograms may provide the clues needed to make the correct decision regarding treatment.[3, 22]

The original rose bengal liver uptake-excretion procedure published in 1955[1] has been used by numerous groups in the United States,[23, 27] Europe,[28, 29] and other areas. The general consensus is that this procedure is a highly sensitive liver function test. Results parallel the clinical picture closely and compare well with the usual battery of biochemical tests. It has also been helpful in distinguishing between medical and surgical causes of jaundice.[3, 22-26] Brown and Glasser,[27] who could not confirm this latter feature, obtained similar uptake-excretion curves from patients with obstructive jaundice and with various types of primary liver disease. They suggested that liver retention measurements be made at 48 and 72 hours because the 24-hour readings frequently had diagnostic value. This report stimulated further studies and led to the development of the hepatogram,[3, 22] which provides the additional data on the time and rates of dye delivery to the intestine; such data are needed for estimating bile flow interference.

Study of multiple liver-test results and repeated hepatograms in ninety-five patients with diseases of the liver and biliary tract in whom diagnoses had been established showed agreement of the hepatograms with the final diagnoses in all but three instances. Moreover, in patients with intermittent or transitory obstruction from stone, the hepatogram has reflected changes in bile-flow interference more quickly and accurately than the alkaline phosphatase and van den Bergh's tests. The BSP and the tracer rose bengal blood clearance tests have approximately equal sensitivity for indicating associated liver injury in jaundiced patients. However, in nonjaundiced patients the rose bengal tracer test is less sensitive than the BSP 45-min. blood-retention test, which is itself a stress procedure when the standard 5 mg./kg. dose is used. Both these tests are more sensitive indices of parenchymal damage than flocculation tests and changes in serum albumin or globulin concentrations. The hepatogram also provides an index of total LVC or the size of the liver vascular bed. The LVC is reduced 30 to 70 per cent in patients with advanced cirrhosis and portal hypertension. This decrease is comparable to the reduction of liver blood flow as estimated in cirrhotic patients by hepatic vein catheterization and BSP liver-extraction techniques.[10, 20, 21]

Further studies are in progress to devise similar external-tracer techniques using radioactive colloidal gold for measuring liver blood flow. Functional disturbances of the portal circulation may be detected by a dual rose bengal blood clearance technique in animal studies as described in this paper. With both of these radiodiagnostic agents and techniques it appears entirely possible to determine the influence of circulatory disorders on the rates of rose bengal blood clearance. Colloidal gold blood disappearance rates are not influenced by abnormalities of polygonal or von Kupffer's cell function when administered in microgram doses, whereas rose bengal blood clearance rates apparently are slowed by polygonal-cell dysfunction and also by disorders of the hepatic circulation.

Kidney studies. In 1955 the radioisotope renogram was developed as a logical corollary to the hepatogram through animal studies using I^{131}-labeled Diodrast and Urokon as test agents.[4] The procedure was then modified for clinical use in 1956.[5, 6] Initial clinical trials with Urokon showed that this agent was handled by mechanisms different from those that handle Diodrast in man, whereas both agents gave similar renal uptake-excretion curves in rabbits.[4-6] With the first clinical trials using Diodrast, the importance of exact kidney localization and of liver interference with the right renogram became obvious, because Diodrast is excreted partly by the liver.[4] When the detector registering the right renogram is directed perpendicularly toward the right kidney, the tracing is influenced by radioactivity simultaneously accumulating in adjacent liver tissue. With the original equipment (FIGURE 1) reliable renograms free of liver interference were obtained by exact kidney localization, using a roentgenogram taken with the patient upright and by positioning the radiation detectors above so that they were directed downward toward the upper poles of each kidney to avoid visualization of the liver. Unless these precautions are taken[4, 5, 6] the right renogram may indicate ureteral obstruction falsely, as a result of liver interference, especially in a patient with liver enlargement or of a short, stocky physique. Other investigators have had difficulty in obtaining reproducible renograms largely because of differences in instrumentation and failure to observe these precautions.

We have attempted to minimize these problems by employing Miokon and Hypaque, which are more organ-specific than Diodrast.[8] With these agents the detectors may be placed in a perpendicular fashion directly over each kidney area without liver interference because less than 1 per cent of the injected dose is extracted by the liver. If collimators with larger apertures (2½ in.) than those used originally (1 in.) are employed, kidney localization is less critical. These changes in radiodiagnostic agents, equipment, and techniques have increased the reproducibility of the renogram while simplifying its performance. The test may be performed routinely without roentgenological kidney localization unless the findings indicate that further investigation is needed. In these few instances X-ray visualization is needed prior to repeating the renogram.

Summary

The rose bengal hepatogram is now established as a highly sensitive liver function test that also supplies diagnostic information on vascular abnormalities of the liver and on the degree of biliary tract obstruction. No other single procedure gives as much useful information for the differential diagnosis and management of patients with diseases of the liver and biliary tract.

The rose bengal-BSP blood clearance stress test is capable of detecting minimal liver damage in rabbits and asymptomatic liver disease in man. However, further investigation is needed for final assessment of its maximum sensitivity.

New tracer techniques using colloidal gold^{198} and rose bengal have been developed in animal studies for further evaluation of liver vascular disorders; both procedures are clinically applicable.

The Diodrast renogram is becoming recognized as a simple, rapid, nontraumatic office procedure for estimating individual kidney functions. It is especially valuable as a screening test for hypertensive patients suspected of having disease of one kidney. Most hypertensives with normal renograms may be spared the discomfort, time, and expense of hospitalization and complicated urological diagnostic procedures.

Recent modifications in the instrumentation and the use of Miokon in place of Diodrast have increased the reliability of the renogram while simplifying its performance.

These tracer tests are unique in providing data on multiple functions simultaneously with complete freedom from drug reactions; radiation exposure is many times less than from X-ray examinations of these organs.

Acknowledgments

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THE EVALUATION OF PHYSIOLOGICAL RESPONSES TO INTRA-ARTERIAL ADMINISTRATIONS OF VARIOUS CONTRAST MEDIA

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The utility of iodine-containing contrast media for venous and arterial visualization has been proved in recent years; for the most part, these media have caused few toxic reactions.

The reactions of a large number of patients to intravenous urographic studies were compiled by Lentino and his co-workers.[1] Two investigations were carried out by Dotter and his associates,[2, 3] one in 1953 on the side effects produced during human angiography and, more recently, one on experimental intra-aortal techniques for use in dogs and humans. These investigators have not only reported valuable techniques, but have also established safety limits for the use of contrast media. Flom and his group[4] and McFall *et al.*[5] have determined the maximal toxic reactions to several contrast agents in dogs, both in terms of lethal dosage and coronary effects. Despite these studies, no simple method of comparing the relative toxicities of several contrast media has come to our attention. The increasing tendency to opacify specific organs demands a continuing awareness of possible adverse responses. Accordingly, we sought a common recordable physiological response of humans and dogs that might be employed for rapid comparative studies.

Preliminary work involved comparisons of the effects of various contrast media upon canine cardiac activity following intra-aortal instillations through a carotid catheter positioned near the coronary ostia.[6] The work employed modifications of techniques previously described by Pearl[7] and Dotter.[3] To avoid the use of X ray the placement of the catheter was manually controlled through an incision in the left thorax between the third and fourth ribs.

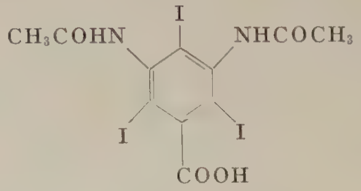
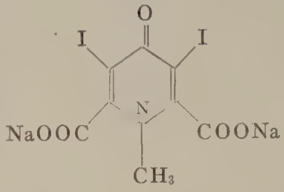
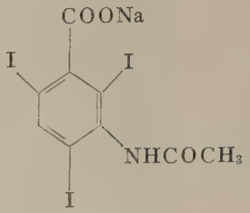
The media used in this study will be referred to by their trademark names to avoid possible confusion from the use of unfamiliar generic designations. The media were administered without dilution; the percentage concentration of total solids and the percentage of iodine present in each of the formulations are given in TABLE 1. Prior to use, the contrast media and injection equipment were heated to 37.5° C. and were maintained at that temperature. For each comparative test the dose volume was constant.

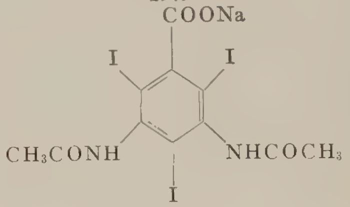
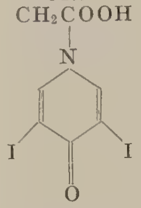
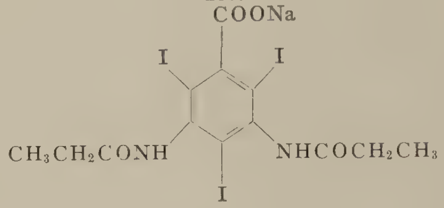
Recordings of the electrocardiographic (Lead II) and hemobaric changes (femoral artery) were made during the repeated intra-aortic injections. In addition, tracings of the longitudinal intestinal movements were made as a possible noncardiac measure of the action of the drugs.

FIGURE 1 shows the recordings from a 10-kg. dog following the rapid intra-aortic instillation of 10 ml. of several of the contrast media, given at 0.5-hour intervals. The saline injection apparently had no significant effects, whereas the media produced a variety of responses. The electrocardiographic changes were fleeting, but the hemobaric and intestinal changes were of longer duration.

TABLE 1

DESCRIPTIONS OF MEDIA USED IN STUDY

Generic name	Sodium and methylglucamine diatrizoate	Methylglucamine diatrizoate	Sodium iodomethamate	Sodium acetrizoate
Trade name	Cardiografin No. 2	Cardiografin	Neo-Iopax	Urokon
Chemical name	Sodium and methylglucamine salts of 3,5-diacetylamino-2,4,6-triiodobenzoic acid	Methylglucamine salts of 3,5-diacetylamino-2,4,6-triiodobenzoic acid	Disodium N-methyl-3,5-diiodochelidamate	Sodium salt of 3-acetylamino-2,4,6-triiodobenzoic acid
Solution, per cent	90.5	85.0	75.0	70.0
Iodine per milliliter, per cent	46.5	40.0	38.6	46.2
Basic chemical structure	 (Free acid) Mol. wt.: 614		 Mol. wt.: 493	 Mol. wt.: 579

Generic name	Sodium diatrizoate	Iodopyracet	Sodium diprotrizoate	Thorium dioxide
Trade name	Hypaque	Diodrast	Miokon	Thorotrast
Chemical name	Sodium 3,5-diacetamido-2,4,6-triiodobenzoate	Diethanolamine salt of 3,5-diodo-4-pyridone-N-acetic acid	Sodium salt of 3,5-dipropionylamino-2,4,6-triiodobenzoic acid	
Solution, per cent	50.0	70.0	50.0	24–26 (suspension)
Iodine per milliliter, per cent	29.9	34.9	28.7	21.0 (Th)
Basic chemical structure	 Mol. wt.: 636	 (Free acid) Mol. wt.: 403	 Mol. wt.: 664	

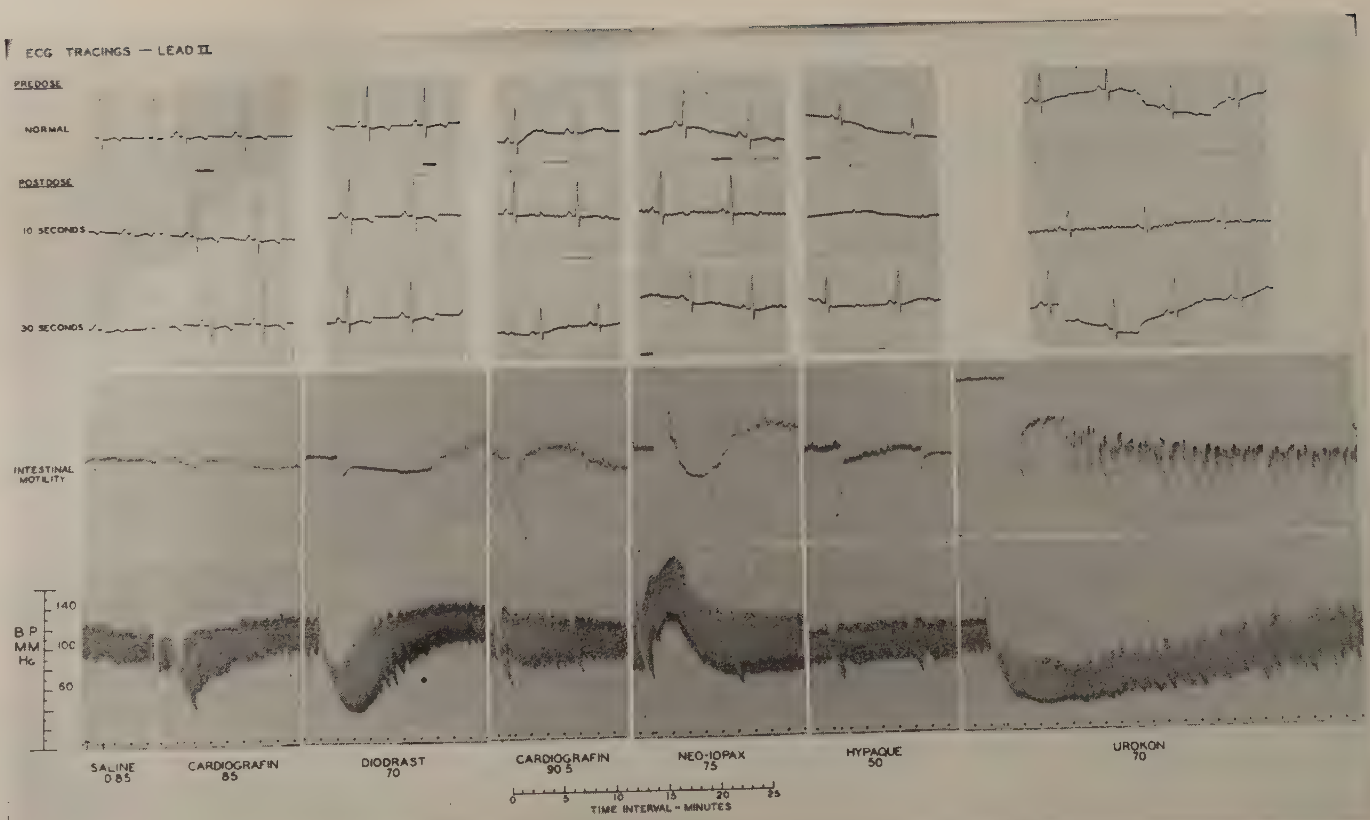


FIGURE 1. The hemobaric, intestinal, and electrocardiographic (Lead II, Cambridge Simpliscribe, 50-mm./sec.) tracings obtained from an anesthetized dog (No. 1) following rapid intra-aortic instillations of 10-ml. doses of various contrast media given at intervals of 30 min.

The bradycardia and prolonged hypotension suggested cumulative toxic effects from excessive doses. The blood pressure changes noted here are reminiscent of those obtained in humans by Dotter in his 1953 study. Another point of interest was the apparent correlation of hypotension with intestinal relaxation and of hypertension with intestinal contraction.

The effects of 5-ml. intra-aortal injections of the contrast media were studied next. The injections were given in a random pattern at 20-min. intervals. Minor electrocardiographic changes were noted (FIGURE 2), the dominant one being a depression of the T-wave that seldom lasted more than 10 sec. Hemobaric and intestinal changes were noted particularly following the injections of Urokon, Diodrast, Neo-Iopax, and Cardiografin 90.5. In the intestinal recording the rapid excursions were diaphragmatic in origin.

Since the cardiac studies were difficult to perform on a routine basis and tended to produce cumulative effects, we investigated the action of representative contrast media directly on the intestinal tract. The effects of 2 to 4 per cent of Urokon, Cardiografin, and Neo-Iopax on isolated strips of guinea pig ileum and rat uterus were nil, and the responses of the guinea pig ileum to barium, acetylcholine, atropine, 5-hydroxytryptamine, and histamine were not affected. The observations suggested that the recorded intestinal changes were secondary to effects upon the intestinal vascular bed. Schobinger and his group,[8] when performing human intestinal arteriography, noted vascular spasms following intramesenteric arterial injections; prior treatment with procaine hydrochloride reduced these effects. In a study of renal function of both humans and dogs, Beall *et al.*[9] observed an alteration in renal hemodynamics during contrast media administration and determined that the primary cause was vasospasm.

Accordingly, we felt that the intestinal changes previously observed, if roughly quantitated, would serve as a rapid, economical, indirect measure of the vascular irritant actions of the drugs.

With a new experimental approach in mind, a terminal branch of the mesenteric artery in a dog was catheterized near the wall of the duodenum (FIGURE 3) so that a polyethylene tube with an outside diameter of 0.024 in. could be passed against the flow to the nearest arterial junction servicing approximately 6 in. of duodenum. Doses of only 0.1 ml. of the various contrast media, administered through this catheter, produced recordable local intestinal movements without causing a detectable systemic effect. Epinephrine (2 μg. in 0.1 ml.) given in like manner, induced relaxation of the intestine.

To prove that a local release of epinephrine was not the cause of intestinal relaxation during the passage of the contrast media, a similar duodenal arrangement with an arterial blood pressure recording (FIGURE 4) was prepared. Two of the radiopaque solutions were injected in 0.1-ml. doses into the mesenteric artery, after which the usual responses were seen. Epinephrine (1 μg./kg.) was then injected into the femoral vein, and the hemobaric and intestinal responses were recorded. This was followed by 2 intravenous injections of Regitine HCl* (0.2 mg./kg. each), a potent antiadrenergic, which inhibited the intestinal

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* Generously supplied by the manufacturer, CIBA Pharmaceutical Products, Inc., Summit, N. J.

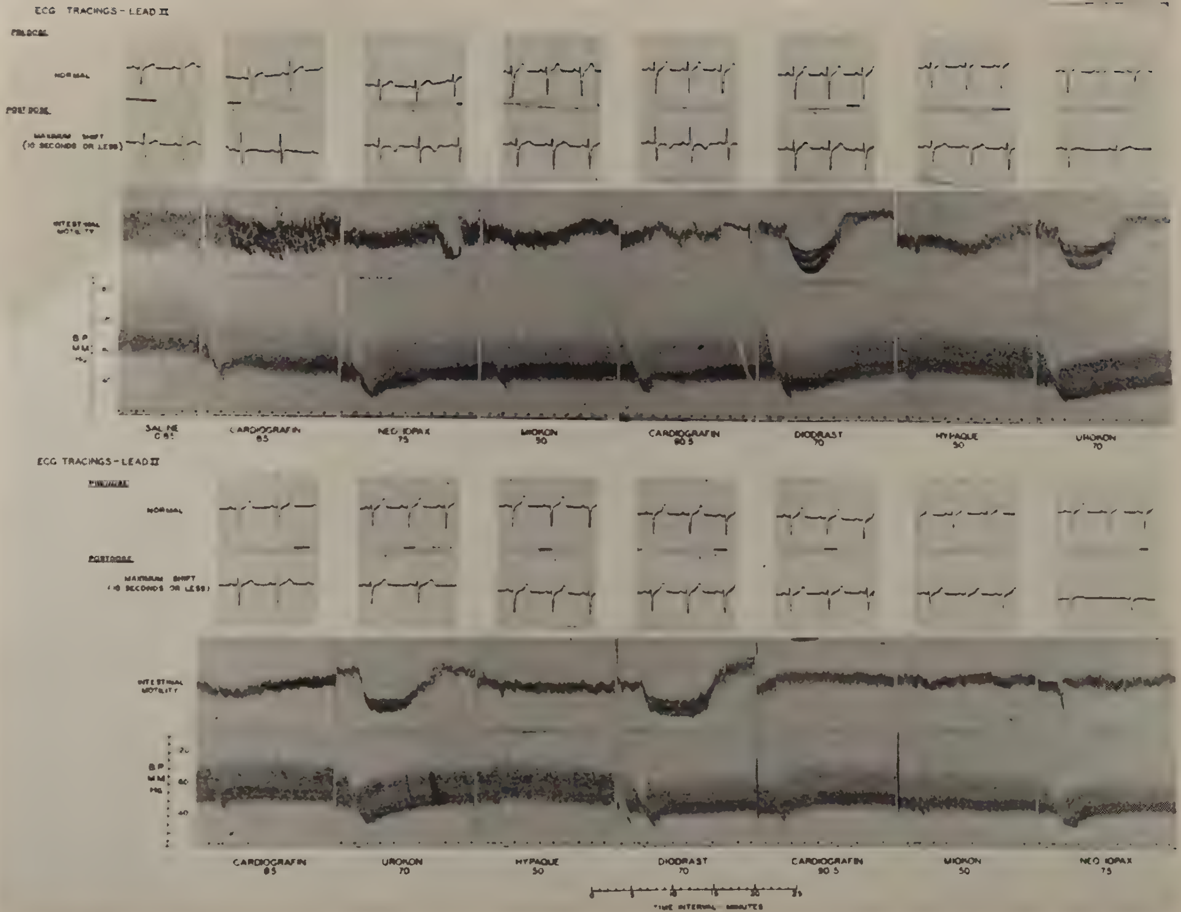

FIGURE 2. The hemobaric, intestinal, and electrocardiographic (Lead II, Cambridge Simpliscribe, 50 mm./sec.) tracings obtained from an anesthetized dog (No. 2) following rapid intra-aortic instillations of 5 ml. doses of various contrast media

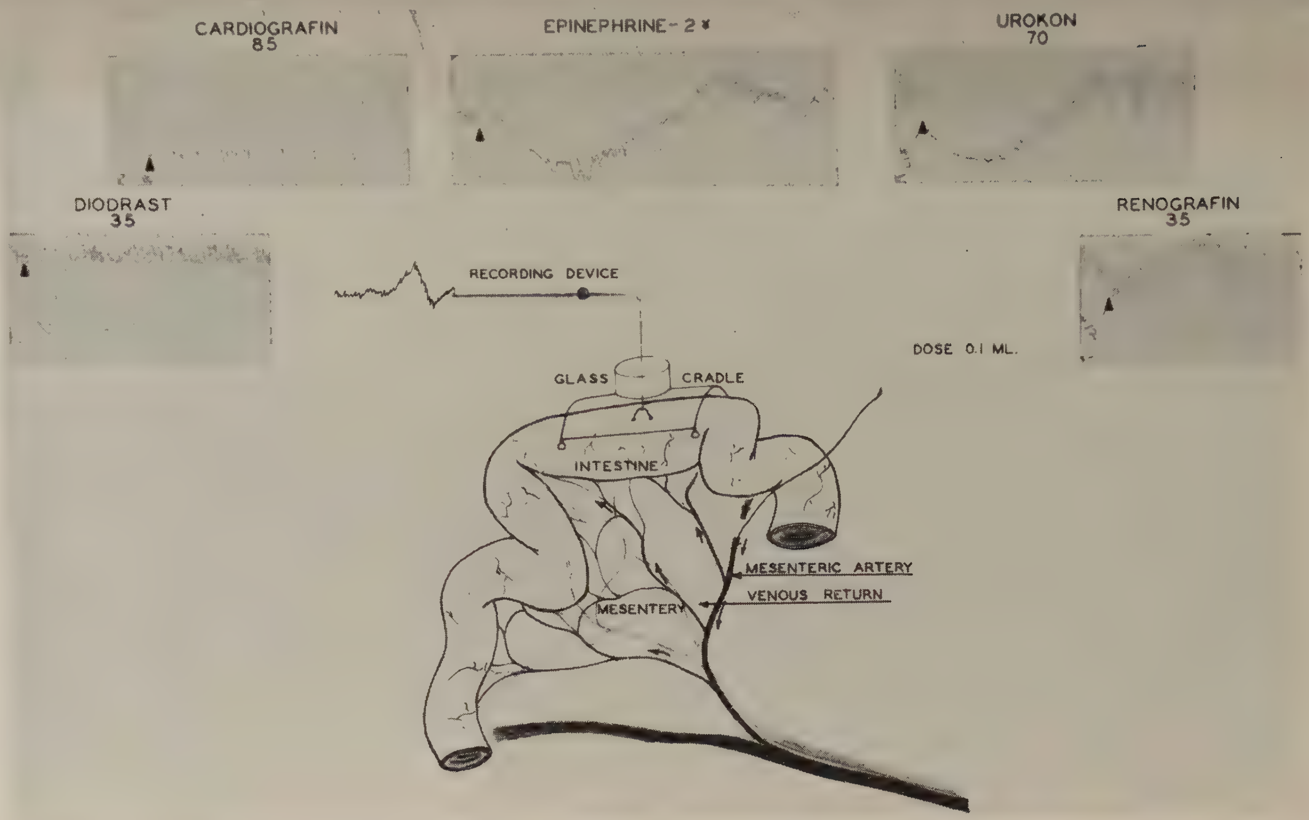

FIGURE 3. A diagram showing the preparation of a terminal branch of the mesenteric artery and a segment of the intestine, and the recordings of the effects of 0.1-ml. injections of a few of the contrast media upon muscular activity.

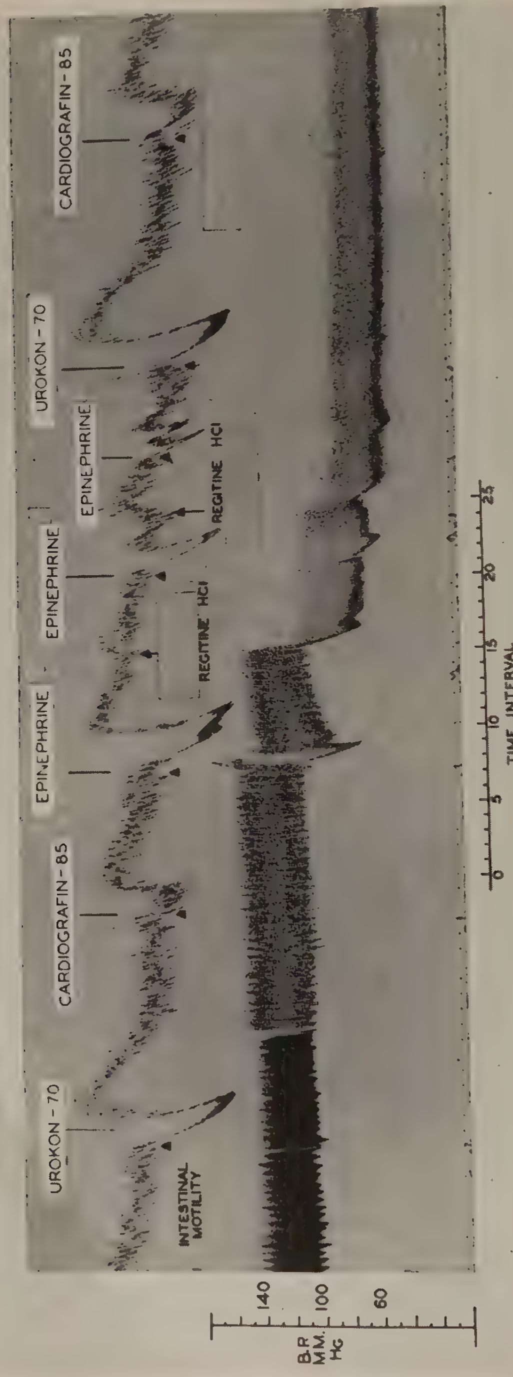

FIGURE 4. The effects of Regitine HCl (0.4 mg./kg. in the femoral vein) upon the intestinal-muscle response to epinephrine bitartrate (1 μg./kg. in the femoral vein) and to injections (0.1 ml.) into the mesenteric artery of 2 representative contrast media.

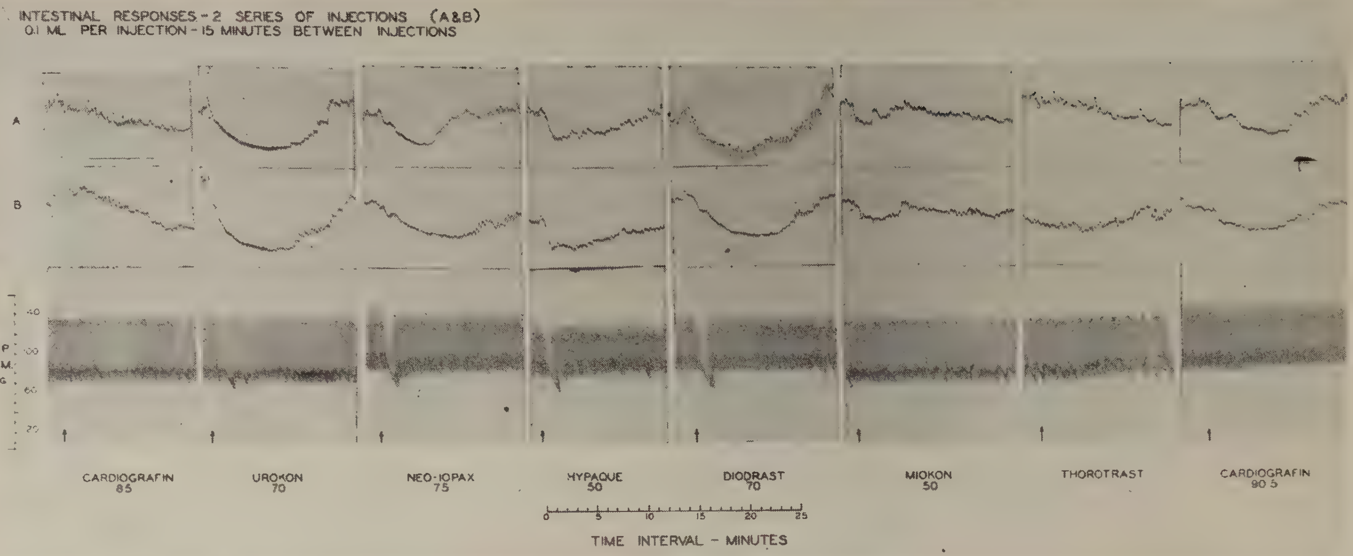

FIGURE 5 The effects upon intestinal activity and the carotid arterial blood pressure (dog No. 4) of 2 series (*A* and *B*) of 0.1-ml. infusions of contrast media into the mesenteric artery, given at 15-min. intervals.

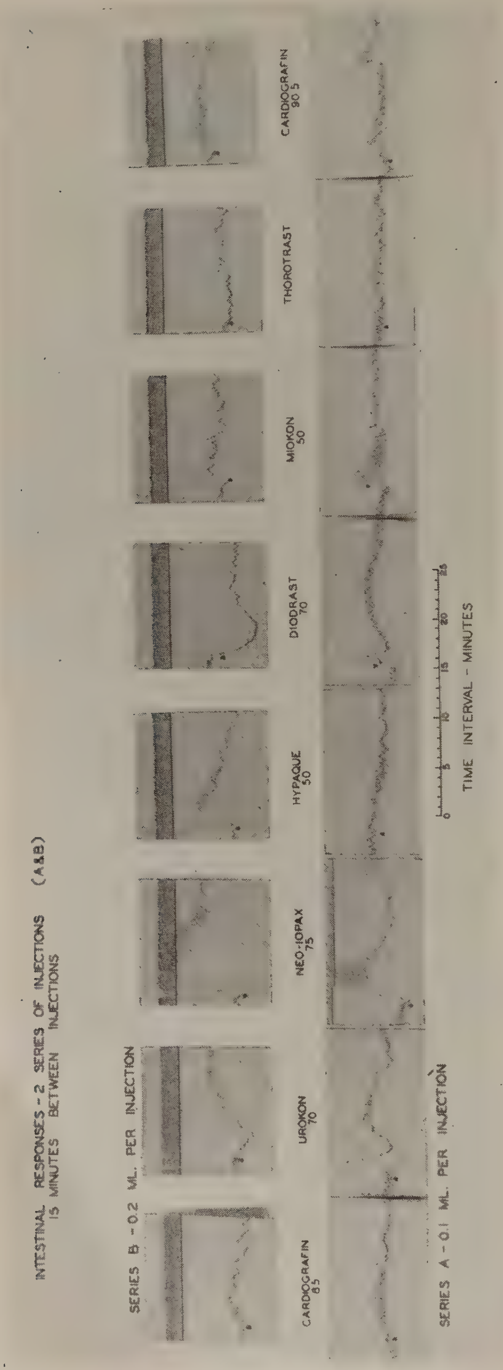

FIGURE 6. The effects upon intestinal motility (dog No. 5) of consecutive mesenteric artery infusions, given at 15-min. intervals in doses of 0.1 ml. (series *A*) and 0.2 ml. (series *B*).

and systemic responses to intravenous epinephrine. Despite this adrenergic blockade, the local intestinal responses to contrast media remained unaltered.

FIGURE 5 shows the intestinal responses to 0.1 ml. intramesenteric arterial injections of each of the various contrast media given twice seriatim to the same dog. This attested to the reproducibility of the responses in the same animal. A prolonged period of intestinal relaxation followed injections of Urokon, Neo-Iopax, Hypaque, Diodrast, and Cardiografin 90.5. Miokon produced some slight relaxation, but Cardiografin 85 and Thorotrast had no significant effects. Some hemobaric changes also were noted as a consequence of the instillations of Urokon, Neo-Iopax, Hypaque, and Diodrast.

In an additional dog (FIGURE 6), 0.1-ml. injections of the various media into the mesenteric artery produced some severe intestinal changes. A prolonged contraction of the intestinal segment was observed with Urokon, Neo-Iopax, and Diodrast, whereas Cardiografin 85 and 90.5, Hypaque, and Miokon produced only transient intestinal activity; Thorotrast had no acute effects. Doubling the doses of the media amplified the responses, but Thorotrast again appeared innocuous. Cardiografin 85 and Miokon produced only slight activity, and Cardiografin 90.5 caused some transient multiphasic movements. Various degrees of more prolonged responses were observed following administration of the remaining media.

Summary

A technique has been presented that utilized cardiac, hemobaric, and intestinal responses in the dog to measure the physiological changes induced by a number of arterially administered contrast media. Vascular spasm was considered to have been the cause of the intestinal movements that, in turn, were recorded as indirect measures of the irritant properties of the contrast media. These same indirect measures appear to provide a rapid, economical method of assessing the anticipated local vascular toxic effects of these media in cardiac and other tissues.

Acknowledgment

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THE APPLICATION OF CINEFLUOROGRAPHY TO X-RAY DIAGNOSIS

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Cinefluorography[1] is a term used to describe the process of taking motion pictures of the fluoroscopic screen of the image amplifier. During the last 2 years we have examined more than 2000 patients with the image amplifier and have taken film strips of more than 1000. All parts of the body usually fluoroscoped have been cinefluorographed. Our experience with the cinefluorographic method should be of interest to those contemplating its use.

Equipment and Procedure

Our cinefluorograph consists of a standard Westinghouse fluoroscope equipped with a Westinghouse image amplifier and a 16-mm. motion picture camera.[2] The image amplifier added to the standard fluoroscope produces a fluoroscopic image so extremely bright that it can be photographed with a conventional motion picture camera.

Cinefluorography is carried out in the same way as conventional fluoroscopy, except that: first, it is not necessary for the eyes of the fluoroscopist to become dark-adapted, saving 15 min. of his time; second, the cone of the fluoroscopic screen is used for palpation, as it is not possible to palpate the patient easily with the right hand.

With this instrument taking motion pictures is easy; the fluoroscopist can do so simply by pushing one lever, since the intensity of the X-ray beam is automatically controlled by a photomultiplier feedback system, and the focal distance of the lens is preset by the serviceman.

Advantages and Disadvantages

As a result of our experience we believe that the image amplifier will replace the standard fluoroscope in the next few years. The real advantages are the production of a bright fluoroscopic image (which allows the fluoroscopist to perceive a more detailed image than that with the conventional fluoroscopic screen) and a smaller radiation dose for the patient. The greater price of the amplifier is the single real disadvantage for the office radiologist. Other disadvantages, such as the weight of the equipment and the small field size, are technical deficiencies that will be soon eliminated.

Just as the image amplifier will replace the standard fluoroscope, the motion picture camera will replace the spot film device. Motion pictures are superior to spot films since both the movement of the organs as well as the static anatomy can be recorded. This superiority of the motion pictures is limited in two respects: the field size is small, and the detail is not as sharp on the projected 16-mm. film as on standard X-ray film. Because of these limitations our attempts at using cinefluorography for angiographic studies on adults have been unsatisfactory.

The Uses of Cinefluorography

In general we have found that cinefluorography is most useful in detecting disease in those areas of the body currently examined by the standard fluoroscope. Our experience has shown that we can detect more abnormalities with cinefluorography than with the standard fluoroscope, for slight alterations in the normal movements of organs can be appreciated more easily.

In the esophagus, certain abnormalities of deglutition, the presence of hiatus hernia, and varices have been more easily detected. Naturally, detailed motion pictures of the process of swallowing are more diagnostic than static spot films.[3] No longer need we struggle to record the fleeting abnormalities of the swallowing mechanism. It is not uncommon now to detect diverticula of the pyriform sinuses. In one instance, a patient showed aspiration of barium into the larynx at the beginning of the swallowing act, only to have the barium expelled from the larynx, without coughing, at the end of the swallowing process.[4] This type of phenomenon is almost impossible to detect by means of conventional fluoroscopy because of the rapidity of the movements involved.

The differentiation between hiatus hernia and normal ampullae has been of particular interest. The entire sequence of contraction and expansion of the distal esophagus aids in separating these entities.

There is no doubt that varices can be detected more readily by this method than by standard spot films. The smaller sized varices may not be apparent except in one phase of contraction of the esophagus. If a single film is not taken in this all-important phase, the varices may be missed.

In the stomach, polyps and ulcers are more easily seen; this is particularly true in a large individual. Recently we saw a prolapsing antral polyp in an extremely large individual. Certainly it could have been detected with the standard fluoroscope, but the chance and ease of detection would have been less. Small variations in the mucosa and areas of slight rigidity of the stomach wall can be noted more readily when a peristaltic wave is passing through the antrum. Actually, the slight residual thickening of the antral submucosa in the healing phase of an ulcer often stands out so prominently on movie strips that we are apt to exaggerate our estimates of these lesions as possibly malignant.

For the first time we have a practical method of recording in the intact individual the peristaltic wave forms of the small intestine. These recordings may prove useful in distinguishing certain physiological states of the small bowel. We were also able to cinefluorograph the contraction and expansion of a Meckel's diverticulum, which contracts when the adjacent bowel is relaxing.

Thus far we have studied only a few colons with the cinefluorograph. Valuable physiological and diagnostic information probably will be obtained through cinefluorography. For instance, the study of peristalsis early in the development of megacolon should prove interesting etiologically.

In the study of the heart and of great vessels, the cinefluorograph is a remarkable tool. We are now cinefluorographing the paradoxical pulsation of the ventricular aneurysm, the increased amplitude of pulsations of the aortic arch resulting from aortic regurgitation, and the remarkable activity of the heart seen in beriberi.

During the last 10 years we have radiographed calcifications within the heart by every known method. Without doubt cinefluorography is the method of choice for detecting and recording these calcifications. Extremely small flecks of calcification, perhaps no larger than 1 mm. in size, can be detected by this method. Diffuse minimal calcification of the left coronary artery can be seen by turning the patient slowly until the artery is on end. Calcifications in the mitral annulus and valve and in the aortic cusps are seen commonly.[5]

Value of Cinefluorography in Instruction[6, 7]

Obviously the teaching value of the film strips obtained through cinefluorography is significant. Previously, a beginning resident in radiology spent many hours peering at the faint fluoroscopic image over the shoulder of his teacher, who would point out interesting and important features, depending upon the patient material. Much of the time of the resident was wasted, but it was the only way he could learn fluoroscopy. This has now changed; our last group of residents was shown a 6 months' compilation of selected cinefluorographic movies of the gastrointestinal tract and heart during the period of introduction to fluoroscopy. The residents quickly became familiar with the normal anatomy, normal movement of organs, and the usual lesions seen during fluoroscopy. Besides this, they were exposed to a remarkable number of current interesting fluoroscopic examinations every day, since all equivocal cases of fluoroscopy are cinefluorographed. These cinefluorograms are shown to the entire staff. At that time the residents can match their skill in observation against the mature skills of the different staff members, and they can also listen to the staff discuss the validity and significance of the fluoroscopic findings.

With the aid of this type of teaching technique our residents appear to be learning fluoroscopic observational skill and judgment more rapidly than their predecessors.

Comment

Our experience suggests that cinefluorography will replace routine fluoroscopy in larger hospitals in the near future. Cinefluorography has proved superior to fluoroscopy in the accuracy of diagnosis.

The small field size and the weight of the instrument are disadvantages that will be corrected soon. The price of the original equipment and the increased maintenance costs will continue to deter the purchase of the cinefluorograph by small radiographic installations.

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STEREOSCOPIC SERIAL ANGIOGRAPHY

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The importance of visualizing the three distinct principal stages in the angiographical exploration of the circulation in a given organ (such as the brain, lungs, and the kidneys) is well known, and has been stated upon different occasions by us, as well as by others.[1-4] The three stages are the arterial (arteriography), the capillary (the most important in establishing an anatomicopathological diagnosis of a lesion), and the venous (phlebography); this latter stage is often clearly divided into two parts.[5] Exploration of these stages of the circulation is accomplished in a different period for each organ.[6] However, the time required remains quite constant for each organ, provided no extraneous factors interfere with the circulation.

The difficulty of obtaining radiographic films of the circulation in its various phases (that is, a complete angiogram) derives from the need for rapid and precise changing of the cassettes.[5,7]

In 1948 we presented at the forty-ninth Meeting of the American Roentgen Ray Society in Chicago our automatic seriograph, capable of changing 12 cassettes at regular intervals, ranging from an 0.5- to 2-sec. picture interval or longer. The device has been widely used in this and in many foreign countries to obtain complete angiograms while varying the intervals between exposures according to the exploration (FIGURE 1).

Contrast Media

Since 1931 we have injected varying amounts of opaque substances in order to establish optimal volumes for different explorations, always considering the opaque substance as a "liquid segment" that must be followed in each passage through the vascular system and recorded on films in the described stages.

Until 1950 the choice of opaque solutions was limited to 70 per cent Diodrast, 75 per cent Neo-Iopax, and 70 per cent Urokon, none of which could be used with impunity, since all are hypertonic and irritating to the endothelium of the vessels, and cause some degree of discomfort.[6]

With Renografin, a triiodinated contrast medium containing 370 mg. of iodine per cubic centimeter of solution, not only is visualization of the vessels excellent but, because Renografin has an almost neutral *p*H, local tissue tolerance is very good, with no reaction and no damage to the endothelium when the injection is intra-arterial. If extravasation occurs, no necrosis or focal inflammation appears. Another important feature of the Renografin solution is the viscosity and the size of the molecule of the diacetylamidotriiodobenzoic acid, which maintains the integrity of the "liquid segment" longer, preventing mixing with the blood.

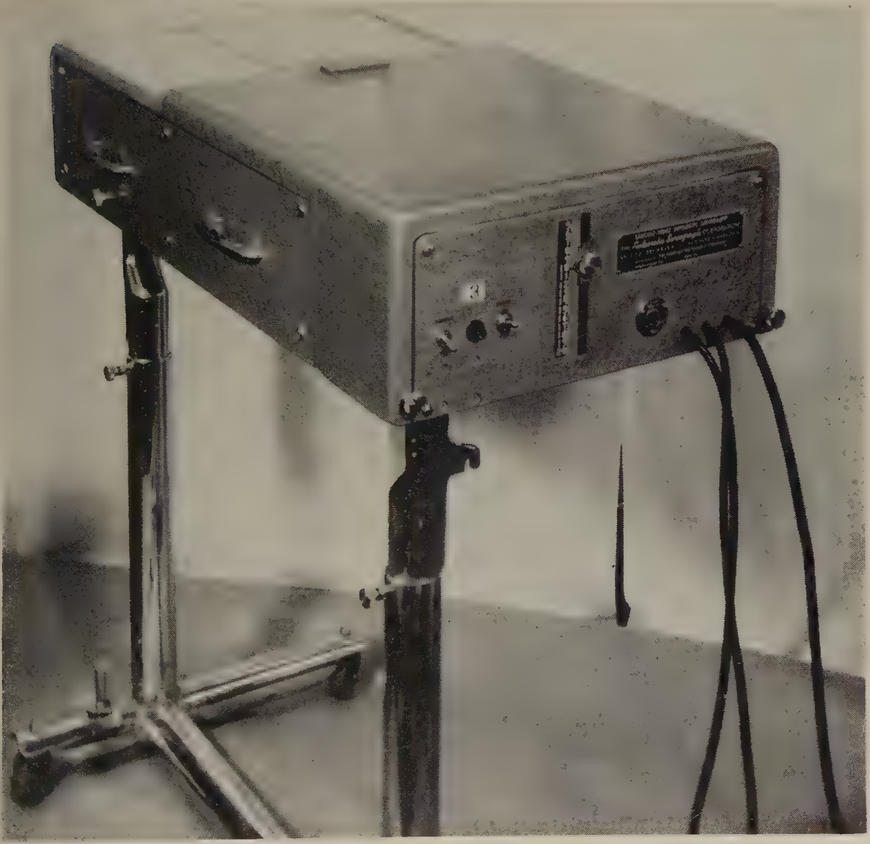

FIGURE 1. The Sanchez-Perez Automatic Seriograph, Model 110.

Stereoscopic Serial Angiography

Once in possession of a reliable technique for obtaining complete angiographic studies in any projection (lateral, obliques, A-P,* or P-A*) and an opaque material of the above-mentioned characteristics, it was desired to develop an automatic stereo-serio radiographic unit capable of performing stereoscopic series for more precise diagnosis.[8,9] This requirement was fulfilled by using 2 tubes (*A* and *B*, FIGURE 2) that make alternate exposures. The 2 identical tubes are placed side by side in such a manner that their focal points remain in the same horizontal and vertical planes 3½ in. apart. The automatic seriograph sends alternating impulses in such a way that tube *B* exposes films 1, 3, and 5, and tube *A* exposes films 2, 4, and 6 of the series. The resulting series of 6 films provides 5 stereoscopic pairs; for example, films 1 and 2, one stereo-

* Anterior-posterior (A-P) and posterior-anterior (P-A).

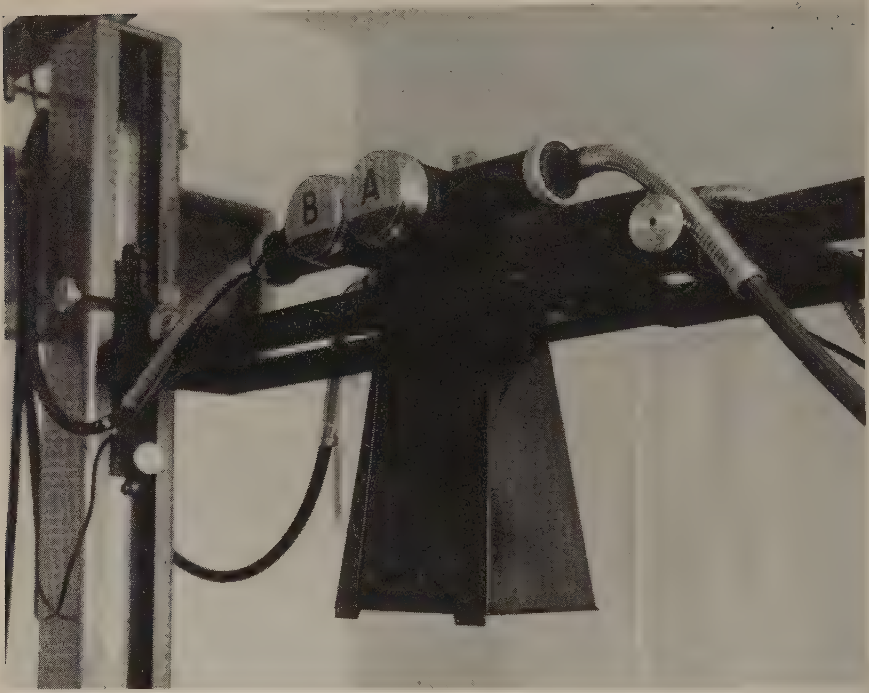

FIGURE 2. View of tubes *A* and *B* perfectly leveled and with the cone protector shown.

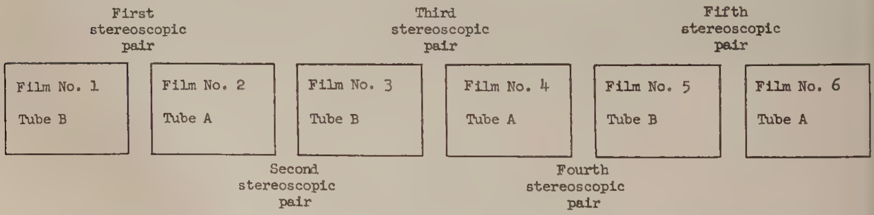

FIGURE 3. Representation of a six-film series forming five stereoscopic pairs.

scopic pair; films 2 and 3, the second stereoscopic pair; and films 3 and 4, the third stereoscopic pair (FIGURE 3).

With the first stereoscopic series we realized the advantages of this procedure, chiefly the elimination of the distortions always present in the lateral, A-P, or P-A views. As is well known, there are no true laterals or true anterior-posterior projections in an angiogram because of the curvilinear pattern of the vascular elements.[10]

It was also obvious that in the great majority of the cases a stereoscopic series is more informative than the lateral and the A-P views together. The fact that the stereoscopic series is obtained with only one injection of opaque material would be in itself a considerable advantage, as most of the complications appear with the second injection of the opaque substance. Reducing the number of exposures to six in each stereoscopic series significantly diminishes irradiation of the patient and the medical personnel.

Stereoscopic Cerebral Angiography

As we have stated elsewhere, every complete cerebral angiogram is formed of 6 exposures taken at regular intervals of 0.7 sec. with the time of exposure 0.05 sec. or less.[11] The amount of opaque material should be 6 cc. when the injection is made in the internal carotid artery, or 8 cc. if the common carotid artery is used; the first exposure is taken when the injection is completed.

When the stereo-serio radiographic unit is used, the above-mentioned conditions remain identical, but the patient is centered over the seriograph at the desired focal distance of 32 in., as the separation between the 2 focal points is 3½ in. In order to obtain a mathematically perfect 3-dimensional effect, we have installed a light beam between the 2 focal points of tubes *A* and *B*, projecting a light spot to the center of the film, where the organ to be explored, in this case the auditory external meatus, should be centered.

Study of the 5 stereoscopic pairs of a stereoscopic serial cerebral angiogram shows that the 3-dimensional effect helps in identifying with certainty the individual vascular elements of the brain, which is otherwise very difficult and, at times, almost impossible in a plane projection. Small vascular lesions that could pass unobserved are clearly distinguished and, when newly formed vessels are present within certain tumors, their architectural arrangement is very distinct.

Case Reports

Case 1. C.D.R., male, age 58 and married, had a 1-year history of nausea in the mornings and frequent headaches for 3 months. Diminution of vision was also experienced, chiefly in the late afternoon. Examination revealed bilateral papilledema, with several hemorrhagic points in the left side; there was also mild facial weakness on the left side. Reflexes of the upper limb increased on the left side and abdominal reflexes diminished on the left side. Left Babinsky was present; on the right side, extensor was not clear.

The stereoscopic cerebral angiogram showed the existence of a multiform glioblastoma in the right parietal region (FIGURE 4*); the diagnosis was confirmed by operation.

Case 2. J. del R. H., male, age 32 and single. Eighteen months before examination by us, headache suddenly appeared on the right side. The patient remained in bed for several days, with dizziness, nausea, vomiting, and slight rigidity of the neck; there was gradual recuperation. At the time of examination a pain back of the right eye was revealed that increased under mild pressure. Ptosis on the right eye was also present, and there was a sluggish pupillary reaction. Gazing up and to the right produced diplopia. There was also paresis of the superior and inferior straight muscles on the right side and anisocoria, with the right pupil larger than the left. The fundus of the eye was normal on the left side and presented a slight degree of papilledema on the right. The tongue deviated slightly to the right.

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* FIGURES 4, 5, 6, and 8 are inserted at the end of this monograph.

The stereoscopic serial cerebral angiogram showed the existence of a very rich collateral vascular net around a zone in which a clotted aneurysm existed (FIGURE 5*).

Case 3. A female, age 50 and married, had suffered for several years from headaches. In the last 18 months unilateral exophthalmos appeared on the right side accompanied by ptosis. The right pupil did not react and the Foix syndrome was positive. Eye examination revealed mild bilateral papilledema.

The stereoscopic cerebral angiogram showed the existance of an ovoidal expanding lesion richly vascularized in the right temporal fossa. Diagnosis of a meningioma was surgically demonstrated (FIGURE 6*).

Stereoscopic Renal Angiography

Every complete renal angiogram is formed by 6 exposures taken at regular intervals of 0.7 sec., with exposure of 0.05 sec. or less. The amount of opaque material injected should be 30 cc., either by percutaneous catheterization of the femoral artery, or by the direct tapping of the aorta on the left side. The first type of injection is indicated when the A-P projection is desired, while the second injection technique gives P-A projections. In either case, the first exposure is taken when the injection is completed.

The patient is centered over the seriograph at a focal distance of 40 in.; the separation between the 2 focal points of tubes *A* and *B* is 4 in. As in stereoscopic cerebral angiography, the series of 6 films furnish us with 5 stereoscopic pairs and, because lateral projection is impossible in renal angiography, the 3-dimensional effect gives us information that could be obtained by no other means.

Case Report

E.P.M., a male, age 64, with a history of pain in the left flank for 6 months and exhibiting proteinuria, became acutely ill with hypertensive vascular disease 3 weeks prior to our examination. Diminished excretory function of the left kidney was proved, and urography appeared to be normal. The patient complained of tiring easily when walking, and of moderate respiratory distress

A stereoscopic renal angiogram was made in the P-A position with 30 cc. of Renografin injected by direct tapping of the aorta from the left side. The 6 usual exposures were taken to obtain the 5 stereoscopic pairs that demonstrated a generalized mild degree of arteriosclerosis of the kidneys and a narrowing of the left renal artery due to intimal arteriosclerotic plaque. The stereoscopic visualization of the right iliac artery showed a partial coarctation (FIGURE 7).

Stereoscopic Serial Pelvic Phlebography

To obtain a complete angiographical exploration of the pelvis we run a second series to visualize the venous elements. Six exposures are taken at regular

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* FIGURES 4, 5, 6, and 8 are inserted at the end of this monograph.

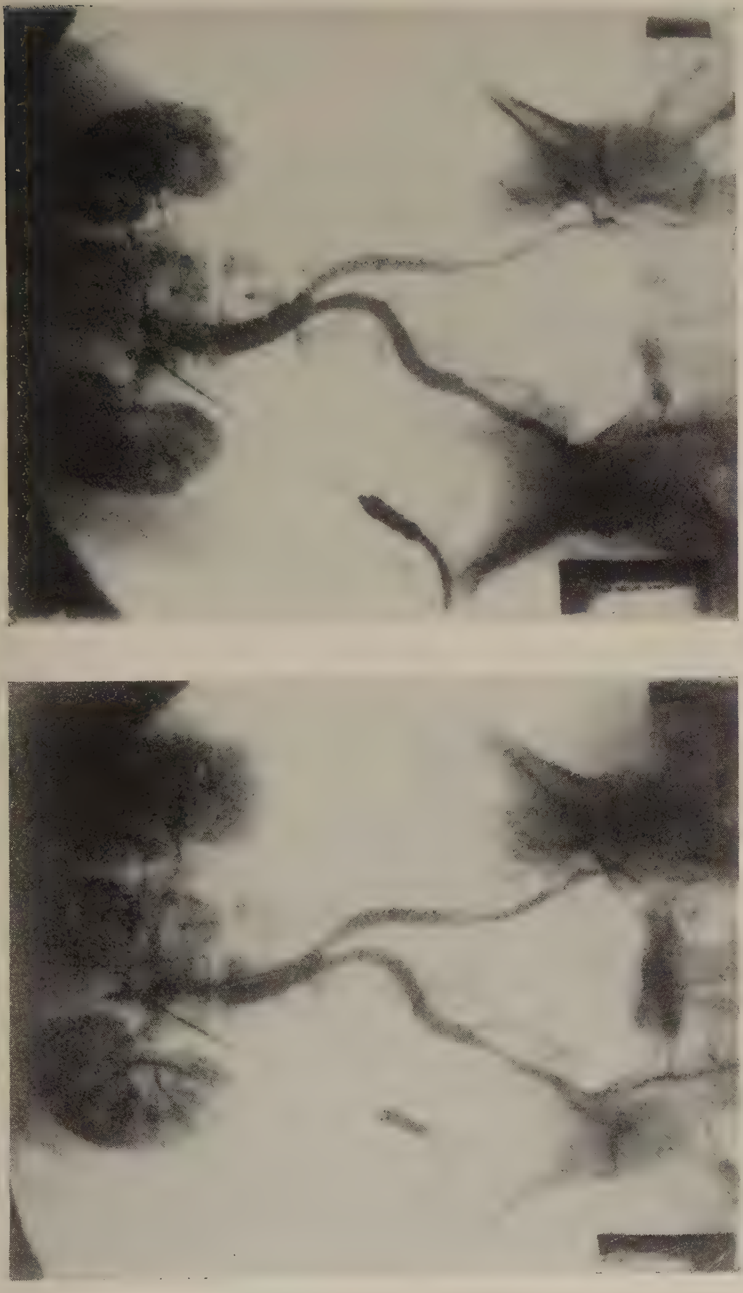

FIGURE 7. Films Nos. 1 and 2 of the series of 6. This stereoscopic pair visualizes a generalized mild arteriosclerosis of the kidneys with narrowing of the left renal artery and with partial coarctation of the right iliac artery.

intervals of 2 sec., with the time of exposure 0.05 sec. or less. The amount of opaque substance is 20 cc. and the injection is made into the marrow bone of the ischium. The first film is taken when 10 cc. is injected. The 6 films obtained furnish us with 5 stereoscopic pairs for study (FIGURE 8*).

Case Report

In O. G. deL., an extremely obese woman, abdominal palpation could not be performed, and gynecological examination was difficult.

Serial pelvic phlebography was used, with local anesthesia of the right ischiatic region after the patient had been placed in gynecological position over the seriograph and under the *A* and *B* X-ray tubes. Focal distance was 35 in.

A 17-gauge needle was nailed into the marrow part of the right ischium with a small hammer. Blood was aspirated with a 10-cc. syringe to prove the proper placement of the needle. Renografin 20 cc. was injected, and a series of 6 films were obtained that gave us 5 stereoscopic pairs in which were visible the right ischiatic and obturator veins and all the venous elements forming the presacral plexus. The opaque material crossed through this plexus to the left side, visualizing the left primitive iliac vein. The fact that the right iliac primitive vein (site of the injection) was not filled proves the existence of an obstacle (tumor) to passage of the opaque material through the right hypogastric vein.

Summary

The benefits to be derived from stereoscopic serial angiography are elimination of distortions; reduction of irradiation for the patient, surgeon, and other personnel; economy in X-ray material; and the use of only one injection of contrast medium for each stereoscopic series.

The cases of five patients who were angiographically explored with the stereo-serio radiographic unit were presented, and final diagnoses were reached.

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* FIGURES 4, 5, 6, and 8 are inserted at the end of this monograph.

PERCUTANEOUS RETROGRADE FEMORAL ARTERIOGRAPHY*

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In 1955 a study of the uses of pelvic arteriography in diagnostic roentgenology was begun at the United States Naval Hospital, St. Albans, N. Y. A simplified retrograde femoral technique was developed and has been employed with more than 200 patients with either obstetrical, gynecological, or vascular surgical problems. A brief analysis of these cases will be presented to indicate the specific clinical uses of this relatively simple radiographic technique.

Historical

A paper by Luschke† demonstrates that the interest in pelvic arteriography existed as early as 1863. Similar studies on the cadaver and postoperative specimens were published in the early part of the Twentieth Century with a classic paper by Sampson[2] in 1912. Not until 1930 was a study done on the pelvic arteries in living subjects; this was performed by Saito and Kamikawa,‡ whose use of the femoral artery was not adopted by dos Santos[4] who utilized the aortogram to visualize the uterine arteries. Coutts,[5] in 1935, also used aortography; both men had good success in demonstration of the placenta. Farinas,[6] in 1941, utilizing retrograde catheterization of the femoral artery, and Hartnett,[7] in 1947, employing translumbar aortography, reported further experience with contrast studies of the uterine arteries in obstetrical and gynecological disease. The induction of labor with aortography and permanent vascular injury with direct exposure of the femoral artery were disconcerting complications.

In 1952, Borell,[3] utilizing the percutaneous retrograde femoral catheterization technique of Seldinger,[8] reported 100 studies on obstetrical and gynecological patients. The complications were limited to hematomas associated with the catheter technique; the clinical importance of the study in placenta praevia and ectopic pregnancies was demonstrated. Further experiences with this technique were reported in excellent treatises by Fernström in 1955 and 1956.[9, 10]

We have used percutaneous femoral arteriography for three years and have encountered none of the complications described above. The rare but disastrous sequelae with translumbar aortography[11-14] do not occur with this technique since, with it, dangerously high concentrations of contrast material cannot enter the spinal, renal, mesenteric, or pancreatic arteries. The procedure is less uncomfortable and, therefore, is better tolerated by the unanesthetized patient. From the beginning of our series the marked value of this technique in vascular diseases was obvious.

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* The views expressed in this article are our own, and they do not necessarily reflect the views of the Medical Department or the Department of the Navy.

† Cited by Borell and Fernström.[1]

‡ Cited by Borell *et al.*[3]

Technique

The only equipment required in percutaneous femoral arteriography is a 16-gauge Lindemann needle and a blood pressure cuff. A serial changer is desirable, but not mandatory. Preparation of the patient consists of omission of the previous meal and administration of 100 mg. of Demerol. In obstetrical

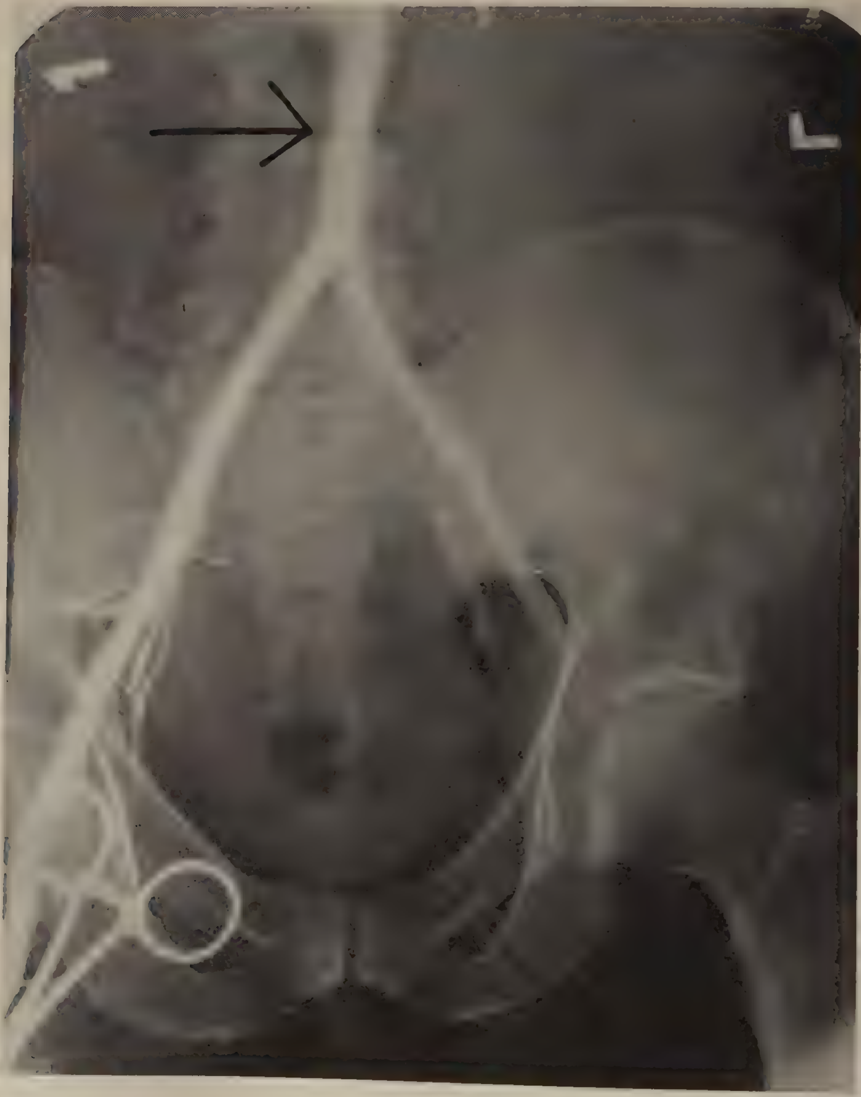


FIGURE 1. A right retrograde femoral arteriogram showing a large plaque of the distal aorta on the right. The contrast column ascends almost to the origin of the renal arteries, but not above this level with hand injection.

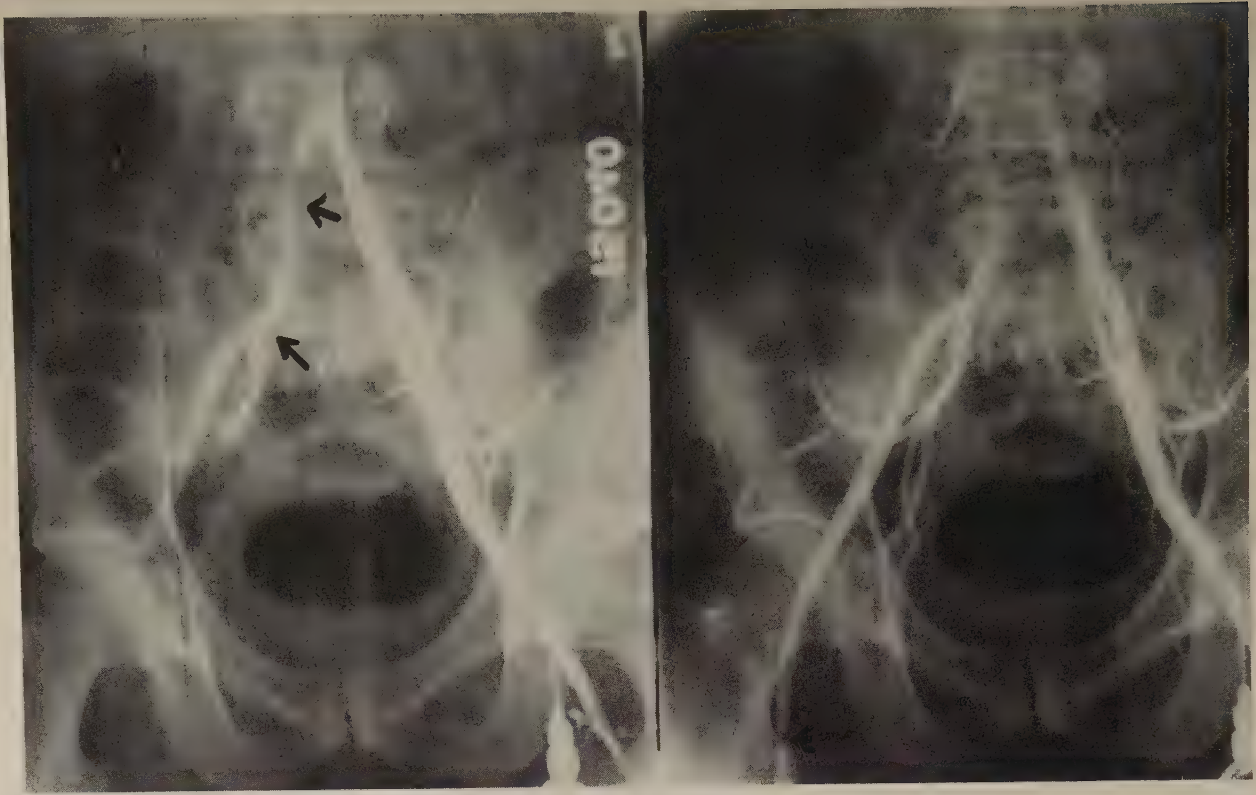


FIGURE 2. A left retrograde femoral arteriogram demonstrating an 80 per cent occlusion of the right superficial femoral and, in addition, severe intimal disease of the right common iliac artery. The distal aorta was normal. Intermittent claudication in the right thigh and leg with good femoral pulses suggested right superficial femoral arterial disease. Note the amount of contrast material in the arterial system on the contralateral side of the injection.

cases, the femoral artery on the side of the placental soufflé is used and, in gynecological cases, the side with the mass or suspected ectopic pregnancy is chosen. In vascular disease the normal or more pulsatile femoral is selected to avoid further injury to the more diseased vessel. A tourniquet is placed cephalad (as far as possible) on the thigh on the same side as the needle. The area immediately below the inguinal ligament is cleansed and, after deep Lidocaine infiltration of the femoral canal, a Lindemann needle is threaded cephalad into the artery; a rubber-covered towel clip fixes the needle to the skin. A serial changer is used for gynecological problems and the table Bucky for obstetrical patients. In vascular surgery the lower aorta, iliac, and proximal superficial femoral arteries are filmed on the serial changer or table Bucky, and the contralateral femoral and popliteal arteries are filmed with a grid cassette and portable machine. In vascular problems, the tourniquet is then removed and a second injection used to visualize the arterial system on the ipsilateral side of the injection. In the pregnant patient, 20 cc. of 50 per cent Hypaque diluted to 30 cc. with saline is utilized. All other examinations are performed with 30 cc. of 50 per cent Hypaque, and the number of injections is limited to 2. A Valsalva maneuver performed by the patient during the forceful hand injection slows the blood flow and gives more time for filming. After removal of the needle, firm pressure is applied for 5 min., and the patient remains in bed for 3 hours.

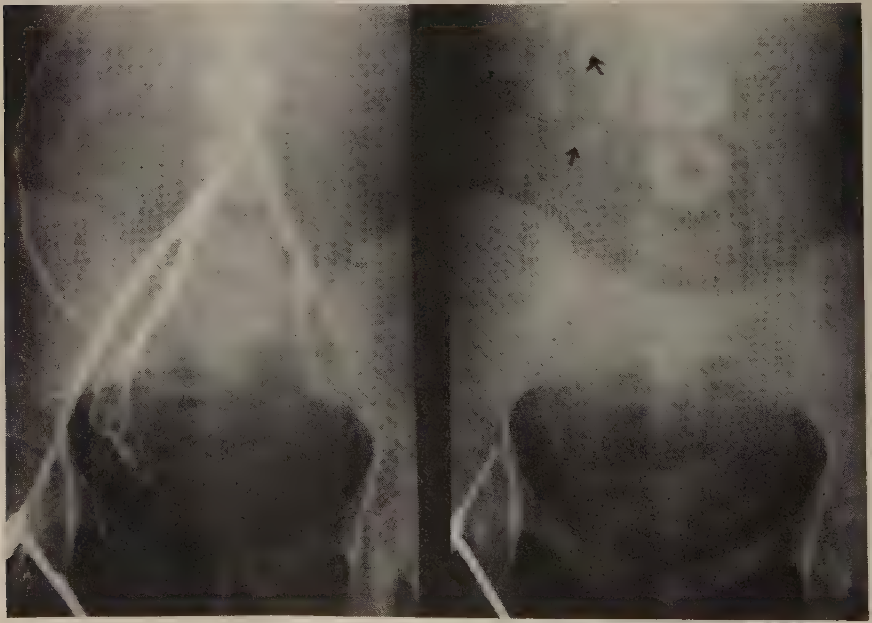


FIGURE 3. A placentogram performed to exclude placenta praevia as a cause for painless uterine hemorrhage in the third trimester. Note the large right uterine artery extending toward the fundus and, at 3 sec. (*right*), the placental sinusoids visualized well above the equatorial plane of the uterus.

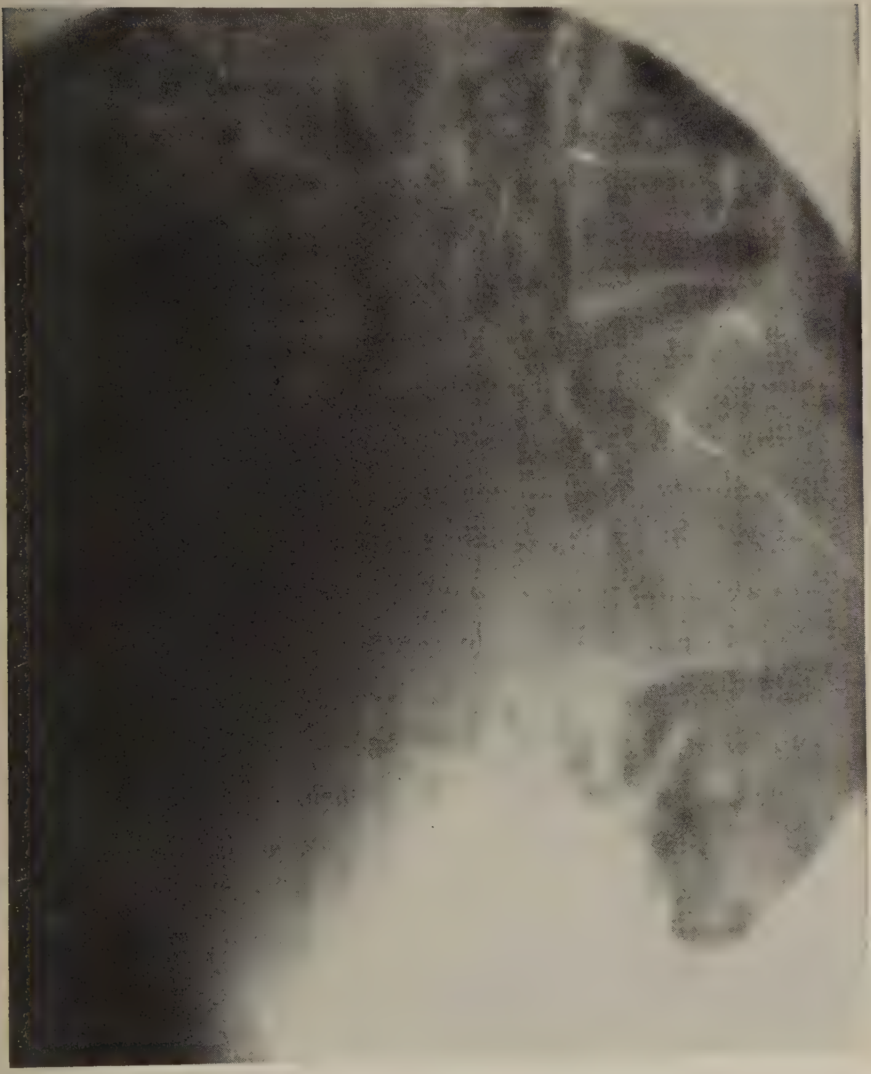


FIGURE 4. Lateral film of the pelvis 3 sec. after a retrograde injection demonstrated a total placenta praevia filling the pelvis. A cesarean section was performed and the diagnosis confirmed.

Clinical Aspects

Although the study reported here was originally begun with obstetrical and gynecological problems in mind,[15] the greatest value has been derived in the field of vascular surgery.[16] Serious complications continue to be reported with aortagraphy despite meticulous technique and the use of smaller volumes and lower concentrations of contrast material. It was for this reason that retrograde femoral arteriograms were performed on a series of patients after their initial examination by aortography. The femoral technique gave better detail of the intima distal to the renal arteries than did aortography. This is explained by the more complete replacement of blood with contrast material, which is due to the retrograde flow. Following this series, aortography was performed only after a complete block was demonstrated by retrograde femoral arteriography. This was done to determine the proximal extent of the block and its relationship to the renal arteries. Postoperative evaluation of grafts is also done by the retrograde technique, utilizing the more normal femoral artery. FIGURES 1 and 2 illustrate the use of this technique in peripheral vascular disease.

In obstetrics the significant causes for painless vaginal bleeding can be detected in more than 95 per cent of cases by means of retrograde pelvic arteriography (FIGURE 3). Of special importance is the exclusion or proof of placenta praevia in the middle trimester (FIGURE 4). At this stage of fetal development, as well as in transverse lies, placentography plays a significant role as a supplement or in preference to soft-tissue techniques. Abruptio placentae produces

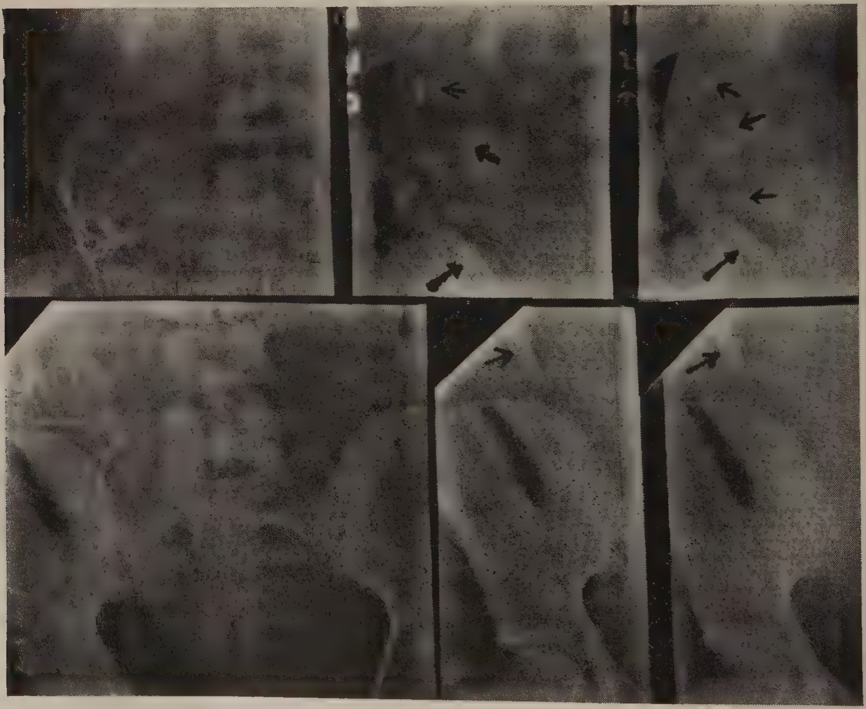
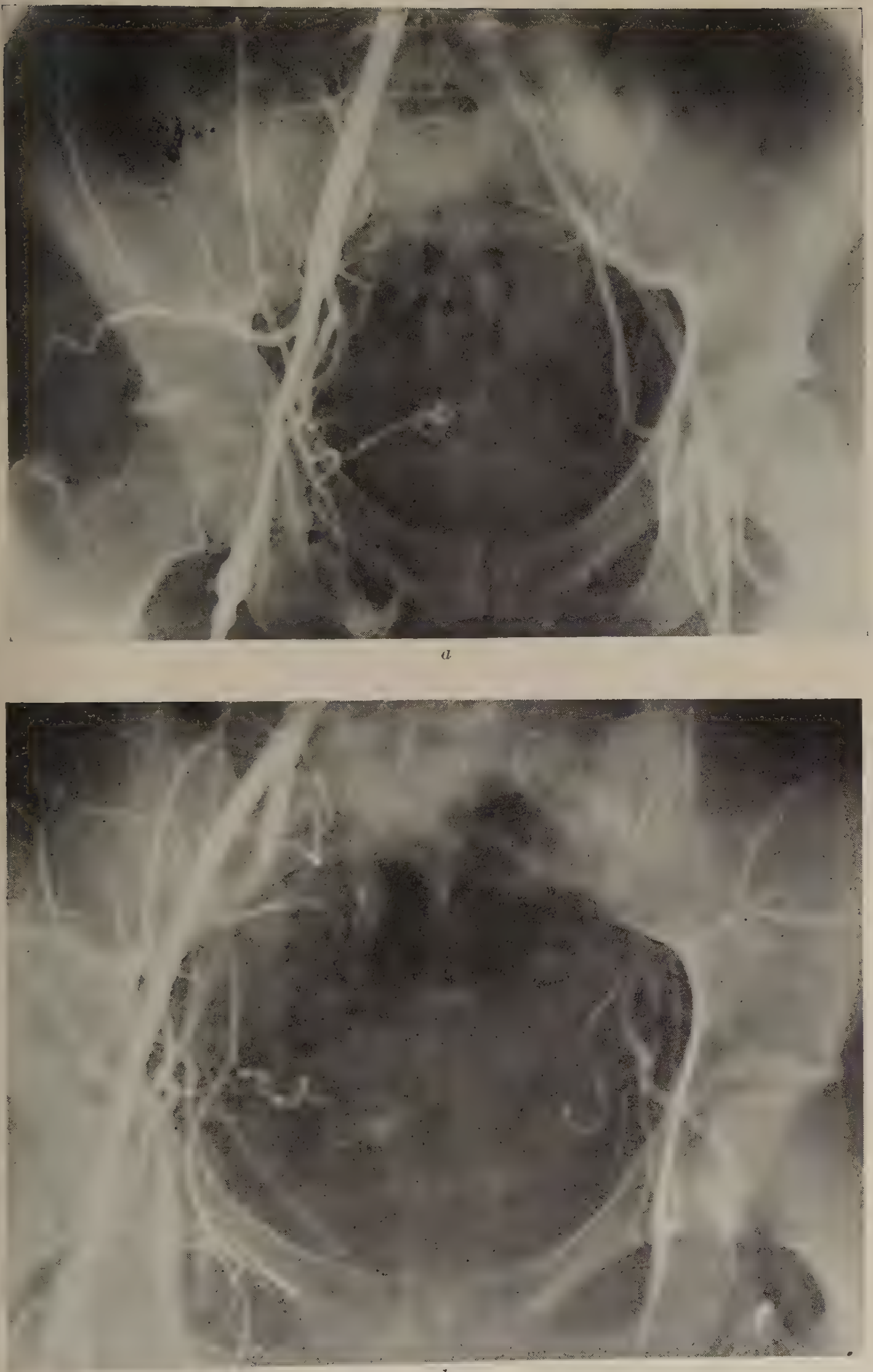


FIGURE 5. A marginal abruptio placentae that subsequent inspection of the placenta confirmed. Note the normal placental sinusoids in the upper right two roentgenograms, with a sharply defined collection of contrast material at the lower periphery of the placenta. Massive uterine hemorrhage during the sixth month of pregnancy prompted this arteriogram.


a

b

FIGURE 6. (*a*) Normal retrograde femoral arteriogram showing the relatively straight uterine artery of the primipara. (*b*) A uterine fibroid on the left side of the cervix displacing the left uterine artery to the left. After a pregnancy the uterine artery, which has been stretched, presents a markedly tortuous course.

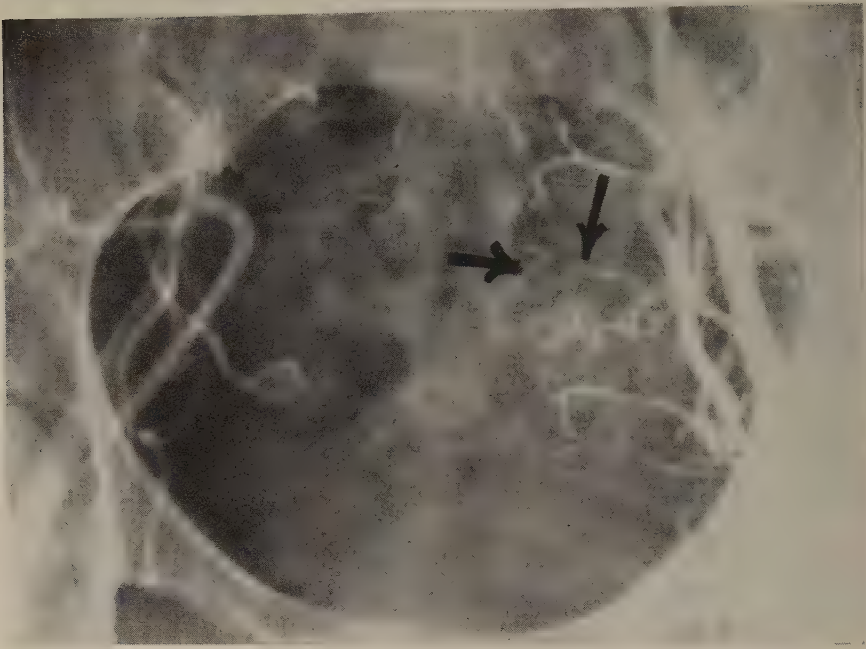


FIGURE 7. A very wide, abnormally located, and straight vessel, which appears at the same time as the adnexal branches of the left uterine artery. This type of vessel is pathognomonic of a uterine fibroid; diagnosis was confirmed by surgery and postoperative injection of the uterus.

a pathognomonic sign that permits positive diagnosis and more intelligent management of the case (FIGURE 5).

In gynecological problems, ectopic pregnancies after the fifth week and uterine fibroids have pathognomonic radiographic signs (FIGURES 6 and 7). Inflammatory and neoplastic tumors of the uterus and adnexa other than leiomyomata do not have characteristic vascular patterns. Only in the very obese patient, when the pelvic examination is inconclusive as to the presence of a pelvic tumor, is pelvic arteriography of value. In these cases pelvic radiographs following pneumoperitoneum with the patient in Trendelenburg's position also permits satisfactory localization.

In our series of more than 200 patients, many of whom had severe obliterative vascular disease, there were no complications. Significant hematomas at the puncture site occurred only once; this was in a postoperative evaluation of a graft while the patient was taking Dicumarol. Firm pressure for 15 min. was the only therapy necessary to control the hemorrhage. Although 60 obstetrical patients were studied in the third trimester, there was no induction of labor and no other adverse sequellae. The rare but severe allergic reactions to organic iodides will undoubtedly be the same as in intravenous pyelography, but none was encountered in this series.

Summary

Experiences with a simplified technique of visualizing the distal aorta, pelvic, and lower-extremity arteries is described. The principal uses for this study have been in the preoperative and postoperative evaluation of obliterative vascular disease and in the management of patients with suspected ectopic pregnancy, placenta praevia, and abruptio placentae.

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INTRAVENOUS AORTOGRAPHY*

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Introduction

With the great advances in vascular surgery that have taken place during the past 10 years, the development of radiological techniques for the accurate visualization of the main arterial channels has become increasingly important. Translumbar aortography, originally introduced by dos Santos in 1929,[1] is still the most widely used technique for demonstrating lesions of the abdominal aorta and iliac arteries, as well as abnormalities in the renal vasculature. Unfortunately, a number of serious complications and some deaths have been reported in connection with this procedure; these include renal insufficiency and anuria, hemorrhage, hemothorax, chylothorax, superior mesenteric artery thrombosis, paraplegia, pancreatitis, adrenal necrosis, and hematoma formation.[2] There also have been rare instances of allergic reaction to the radiopaque contrast material. Furthermore, many institutions, including the University of Minnesota Hospitals, Minneapolis, Minn., deem it wise to perform all translumbar aortograms under general anesthesia with an endotracheal tube in place, adding expense and morbidity to the procedure.

Inasmuch as most of these complications have been due to the blind puncture of the diseased aorta, other approaches to this problem have been employed; these have included both forward and retrograde catheterization via the left ventricle and aortic arch, the brachial artery, the subclavian artery, and the femoral artery. Excellent visualization of the abdominal aorta and its branches may be obtained by these procedures in most cases. However, all involve the use of a delicate operative procedure requiring a fully equipped operating room and the presence of a skilled surgeon. The risk of an arterial puncture and the possibility of subsequent thrombosis of the vessel punctured are still present, and the most commonly used retrograde femoral artery catheterization technique is difficult to employ in patients with advanced stages of arteriosclerosis involving the ileofemoral vessels.

Because of these difficulties, many institutions have given up the practice of routine aortography in patients with abdominal aortic aneurysms that seem obvious on physical examination. Indeed, most of the current surgical literature indicates that arteriography is both needless and dangerous in these cases. However, erroneous preoperative diagnoses of abdominal aneurysms have been made on the basis of physical examination alone and have led to unnecessary surgical exploration. These unnecessary operations certainly emphasize the value of preoperative aortography.

It is felt, therefore, that a method of aortic visualization involving the venous injection of radiopaque contrast material would be of considerable value. It is our purpose to present some of the clinical applications of a method currently employed at the University of Minnesota Hospitals.

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Development of the Procedure

In some of the early studies involving the use of rapid intravenous injections of contrast media for angiocardiography, Steinberg noted that the renal shadows were also opacified.[3] In 1947 Weens and Florence[4] made use of this observation and of a balloon to obstruct the ureter in order to develop a satisfactory technique for nephrography. This technique was developed further and refined by Evans[5] and his group in 1955, when they introduced the use of Decholin circulation times to determine with accuracy the desired interval between injection and film exposure. In addition, they combined tomography with their nephrograms—nephrotomography. Van Velzer and Lanier[6] simplified the circulation-time studies, using a tracer dose of radioactive iodine injected intravenously and scanned over the kidney region. In reporting their work both these groups have indicated that they were occasionally able to visualize segments of the abdominal aorta.

It seemed logical to combine the use of I^{131} circulation-time studies, rapid intravenous injection of concentrated opaque material, and serial biplane radiography in an attempt to demonstrate the abdominal aorta.[7] Early studies in dogs were successful; however, in our initial studies in patients we were unable consistently to visualize the aorta. These first human studies were performed with 50 cc. of 90 per cent Hypaque injected intravenously through a No. 13 or No. 15 needle as rapidly as possible with an ordinary 50-cc. syringe—the technique used for nephrotomography.

To increase the concentration of radiopaque material in the aorta, three adjuncts have been employed: (1) a polyethylene catheter has been placed through a cut-down in the medial antecubital vein; (2) a steel syringe and lever injector are now employed; and (3) blood pressure cuffs are placed around all the extremities and inflated to a pressure exceeding the patient's arterial systolic blood pressure during the time of injection and actual film taking. In addition, the dose of contrast material has been increased to between 60 and 80 cc.

Technique

A cut-down is made into the right median antecubital vein and a polyethylene catheter of internal diameter of 0.106 in. is inserted for a distance of 6 to 8 in., to the region of the axilla. Isotope circulation time to the abdominal aorta is then accomplished. I^{131}-labeled Renografin* (50 μc.) is mixed with 2 cc. of stable 76 per cent Renografin and layered in front of 50 cc. of saline in the steel syringe of the Elema Schonander lever injector. The stable 76 per cent Renografin holds the less dense radioactive material in a layer and, if care is used in handling the mixture, the entire radioactive bolus remains together. We feel this is of considerable advantage in accurate timing, since the counter held over the peripheral vessel will record a sharp rise at the time of the initial appearance of the bolus rather than a more delayed, gradual rise that results if the radioactive material is diluted before injection. The 50 cc. of saline solution is used to approximate the volume of contrast medium to be injected later. A considerably slower circulation time will be obtained if only 1 or 2 cc. of radioactive material is injected.

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* Prepared for and supplied to us by the Squibb Institute for Medical Research, New Brunswick, N. J.

The mixture is then rapidly injected with the lever injector, and the interval between injection and appearance at the vessel of interest is determined by use of a collimated scintillation counter, a scaler, a Berkeley Computing Ratemeter, and an Esterline Angus recorder. The warmed contrast material is then injected as rapidly as possible (within 2 sec.), and films are exposed after injection at an interval determined by the circulation time. For these studies we have used 90 per cent Hypaque,* 85 per cent Hypaque, and 85 per cent Cardiografin.† Our experience is not sufficient to enable us to detect a significant difference in the quality of visualization obtained with these agents. However, we find the 85 per cent Hypaque considerably easier to inject than the more concentrated 90 per cent material.

The majority of the studies have been performed utilizing the Schonander biplane rapid changer. Films have been exposed at 1 per second in the A-P plane, beginning approximately 1 sec. earlier than the arrival of the radioactive-tracer dose. In addition, 4 or 5 films have been exposed in the lateral plane at 2-sec. intervals. In an effort to make this technique more generally practicable for less elaborately equipped hospitals, several patients have been studied using 1 long exposure. Exposure times of between 5 and 8 sec. have been used on a single 14- × 17-in. film, in both 1 and 2 planes. An advantage to the latter method, in addition to its obvious simplicity regarding film and equipment, is the fact that the field size is 3 in. longer than with the standard Schonander changer. While it may be difficult for some patients to hold their breath for this length of time (causing some of the details of the study to become blurred), satisfactory visualization of the aorta and its main branches has been achieved. Further refinements in X-ray technique are being carried out, and we hope to end with 2 or 3 large films of the aorta and its major branches, each film representing a relatively short exposure.

Following the completion of the intravenous aortogram, a routine intravenous pyelogram is obtained.

Results

Forty-one patients have been examined by this method. Satisfactory visualization of the abdominal aorta and its major branches has been obtained in 36 of the 41. The patients' ages ranged from 29 to 78 years; most of the patients were between 50 and 70 years of age. In 4 of the 6 patients in whom satisfactory visualization was not obtained, a malfunction of the rapid film changer was responsible and, in 2 cases, the amount of contrast material in the abdominal aorta was so faint as to preclude accurate diagnosis. In 5 patients, second injections were made. Four of these were made the day after the original procedure, and 1 was performed 7 hours after the first study. No unusual symptoms were noted in these cases.

No serious reactions to the contrast material have occurred. All patients experience a generalized sensation of warmth and a metallic taste, but both

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* Supplied by Winthrop Laboratories, New York, N. Y.

† Supplied by E. R. Squibb & Sons, New York, N. Y.

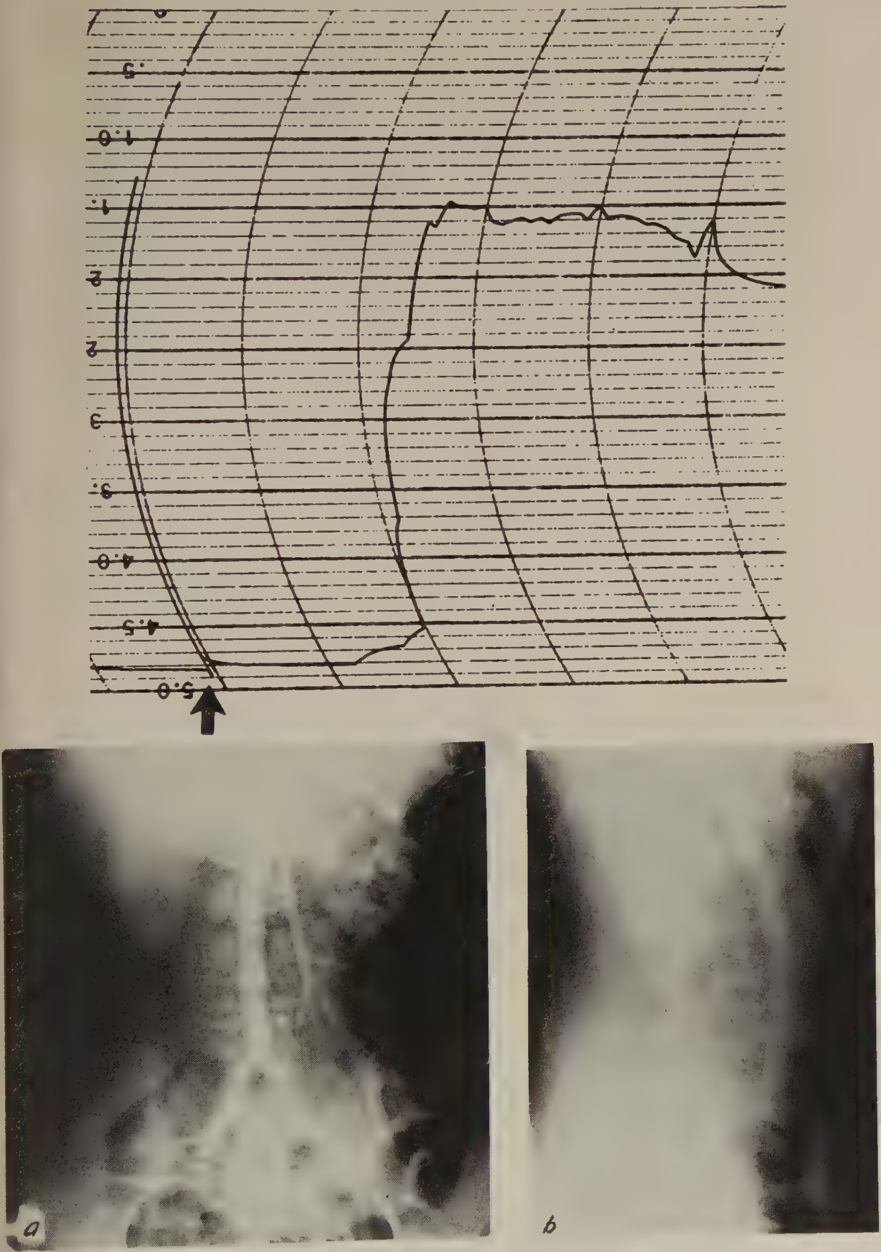

FIGURE 1. Top of page: normal I^{131}-Renografin tracing (Case 1). Arrow indicates injection. Time of appearance, 7.5 sec. (*a*) Normal I.V. aortogram (Case 1). Note dense superior mesenteric artery opacification. (*b*) Normal lateral projection. Note splenic and superior mesenteric arteries anterior to aorta.

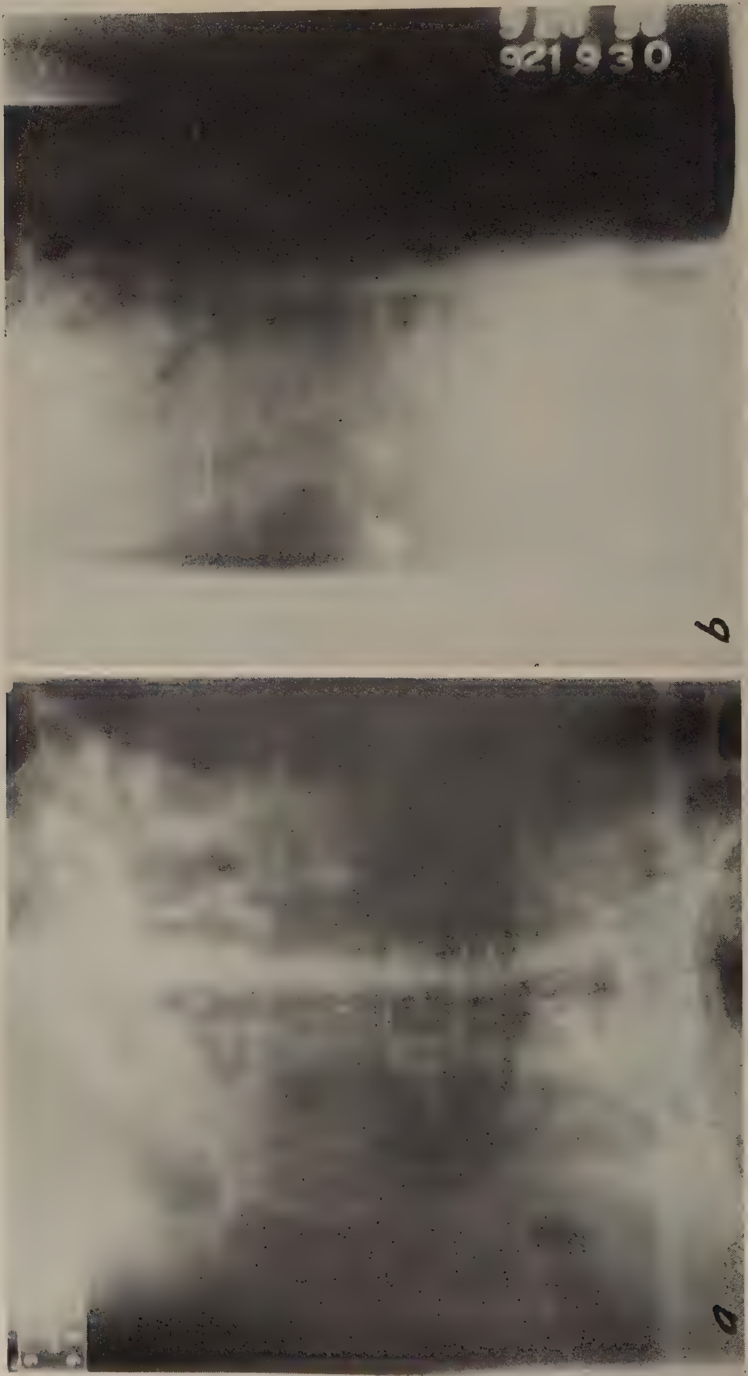

FIGURE 2. (*a*) Normal, A-P view. (*b*) Normal, lateral view (both Case 2).

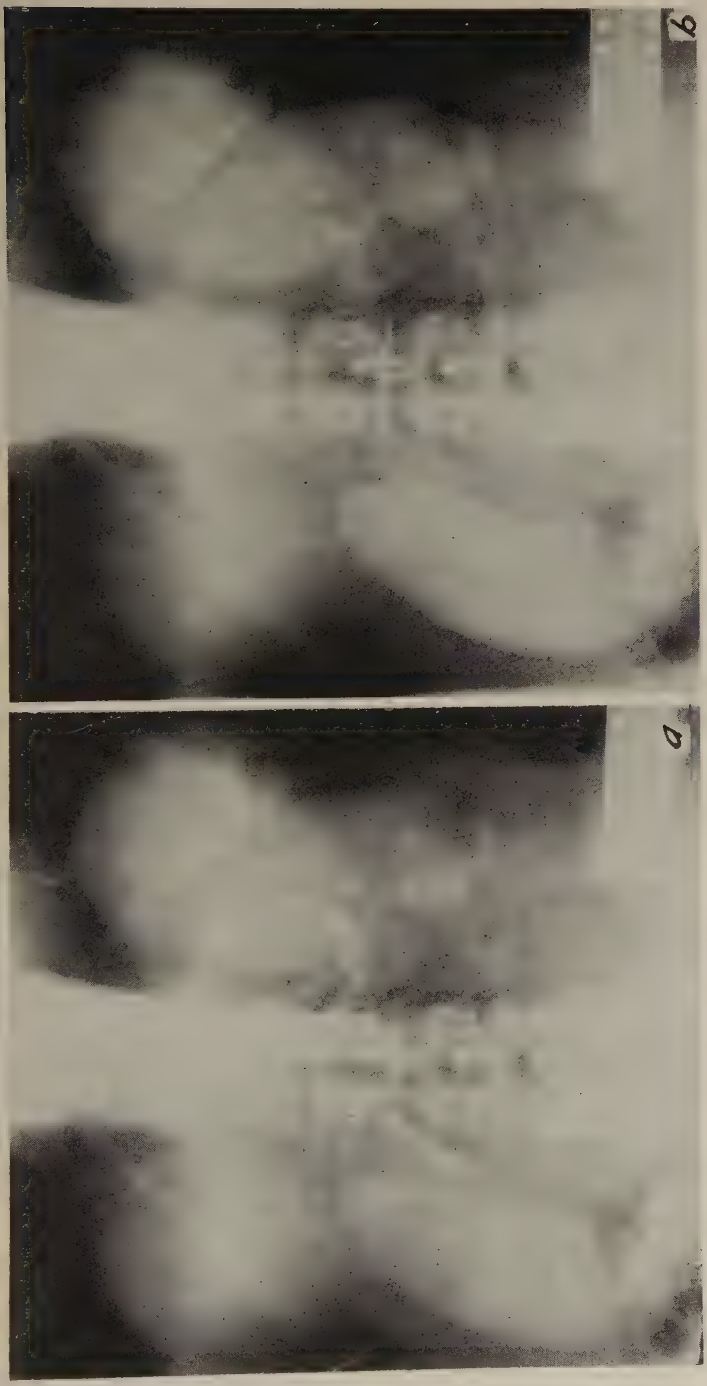

FIGURE 3. (*a*) Low right kidney; normal study. (*b*) Nephrographic phase. Note density of spleen as well as kidneys (both Case 3).

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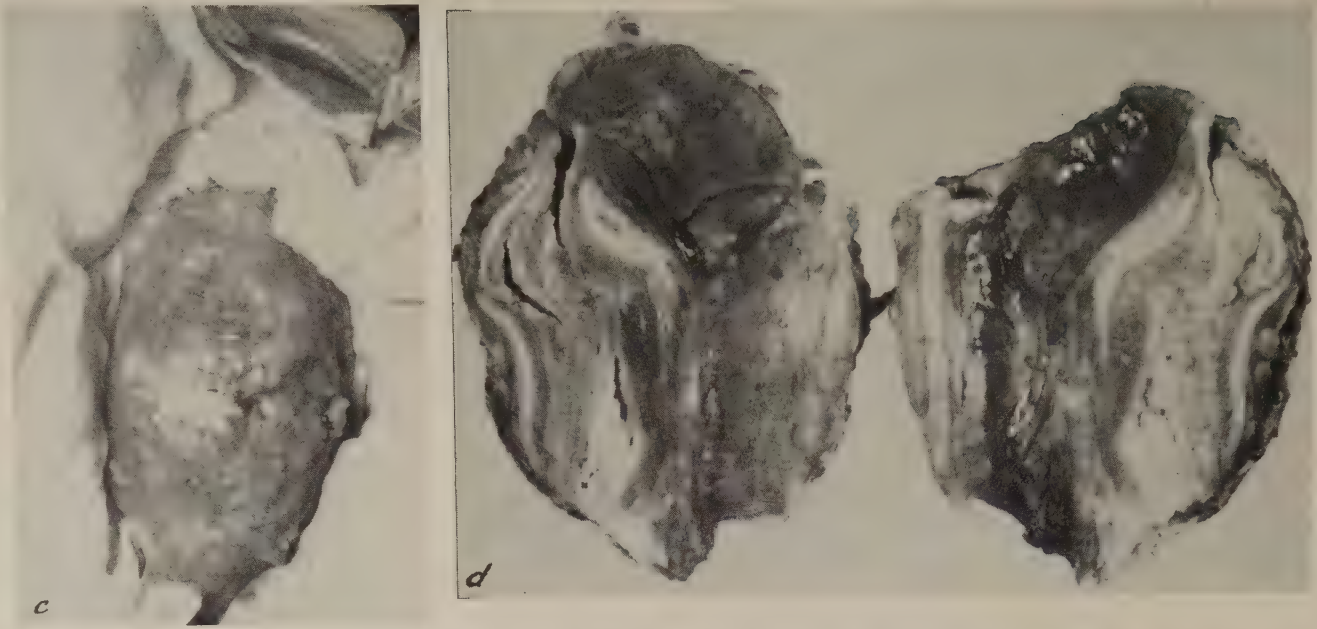


FIGURE 4. (*a*) Aneurysm of abdominal aorta. Note soft-tissue density below contrast-filled portion of aneurysm. (*b*) Lateral view. (*c*) Aneurysm at surgery. (*d*) Aneurysm cut longitudinally. Note large lamellated clot (all Case 4).

of these symptoms are fleeting. Two patients experienced nausea, but there was no vomiting, and 1 developed a mild headache that lasted for 15 min.

Illustrative Cases

Case 1: normal aorta. A 54-year-old, white female entered the hospital for surgery for varicose veins. There had been several episodes of thrombophlebitis, and her abdominal aortic pulsations were felt to be more prominent than normal. Following a labeled Renografin tracer study (FIGURE 1 *top*), an intravenous aortogram was performed, which was normal (FIGURE 1*a*, *b*).

Case 2: normal aorta. A 65-year-old woman entered the hospital with markedly increased abdominal pulsations. A clinical diagnosis of possible aortic aneurysm was made. Intravenous aortography revealed a normal aorta and normal major branches (FIGURE 2*a*, *b*).

Case 3: normal nephrogram. A 58-year-old female had a mass in the right lower quadrant. A renal neoplasm was suspected. Intravenous aortography (FIGURE 3*a*) revealed a low-lying right kidney that appeared normal and showed a good visualization of the abdominal aorta and its major branches. The nephrographic phase (FIGURE 3*b*) was exposed 6 sec. after the initial film. A follow-up intravenous pyelogram was normal.

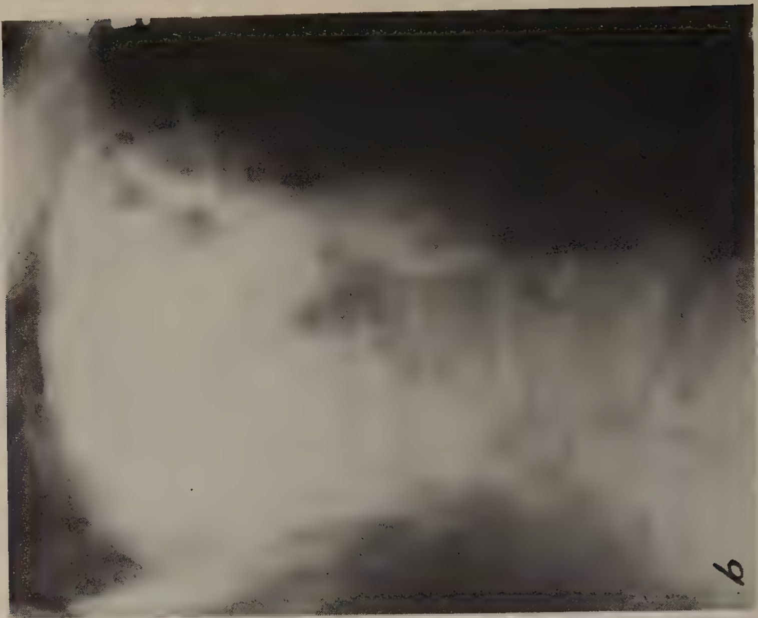
Case 4: aortic aneurysm. This 69-year-old male had a pulsatile mass in the left mid-abdomen. Intravenous aortography (FIGURE 4*a*, *b*) showed an aneurysm of the abdominal aorta distal to the origin of the renal arteries. Careful inspection of the films showed a faint calcific rim extending below the area opacified by the aortogram down toward the bifurcation of the aorta. A large aneurysm was resected at surgery and a graft inserted. The aneurysm contained a large amount of lamellated clot (FIGURE 4*c*, *d*).

Case 5: aortic aneurysm. This 76-year-old male complained of a pulsation that had been present in his upper abdomen for 4 months. A pulsating mass could be felt, but it could not be determined if the pulsations were expansile or transmitted. Intravenous aortography revealed an aneurysm of the abdominal aorta (FIGURE 5*a*, *b*). A resection of the aneurysm with replacement by a Teflon bifurcation graft was done (FIGURE 5*c*, *d*). A repeat intravenous aortogram, done 1 week after surgery, revealed good function of the graft (FIGURE 5*e*, *f*).

Case 6: iliac thrombosis. This 29-year-old diabetic female had had (2 years previously) a below-knee amputation on the right as a result of vascular insufficiency and gangrene of the foot. Re-entry to the hospital was caused by claudication and ischemia in the left leg. Intravenous aortography showed irregularity at the distal aorta and a block at the origin of the left common iliac artery (FIGURE 6). Findings were confirmed at operation, and a graft was inserted.

Case 7: femoral artery thrombosis. This 72-year-old male had claudication in his right leg for 5 months. Intravenous aortography was performed utilizing a single 6-sec. exposure with two 14 × 17 cassettes, 1 under the abdomen, and 1 under the thigh and leg. The aorta and iliac vessels were shown to be patent. There was a block at the origin of the superficial femoral artery on the right, with a patent profunda femoris (FIGURE 7).

FIGURE 5. (*a*) Aneurysm of abdominal aorta. Faint nephrogram on right is due to fogging from simultaneous lateral exposure. (*b*) Lateral view. (*c*) Aneurysm at surgery. (*d*) Teflon bifurcation graft at surgery. (*e*) Postoperative I.V. aortogram. Note low position of iliacs. (*f*) Lateral view (all Case 5).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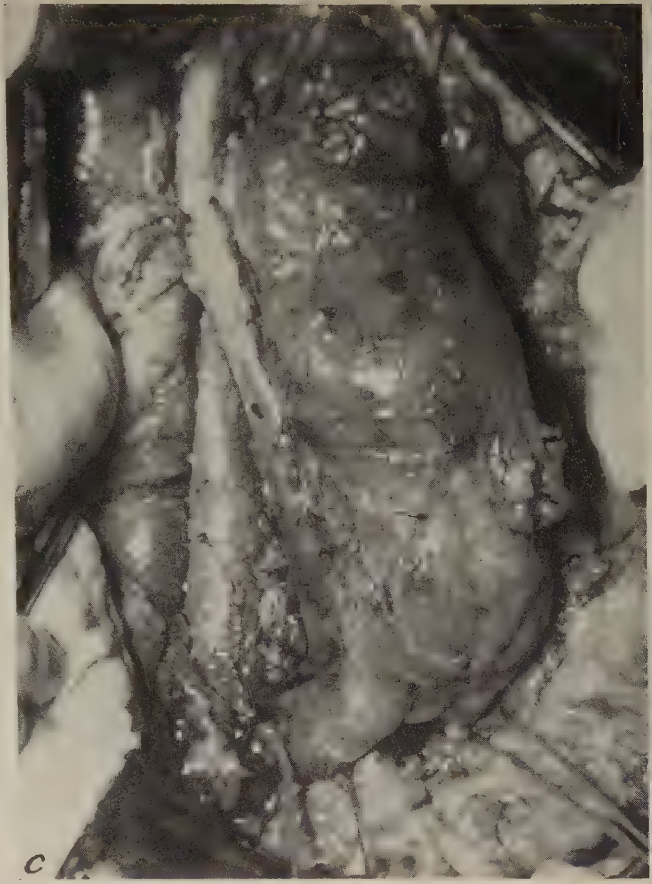
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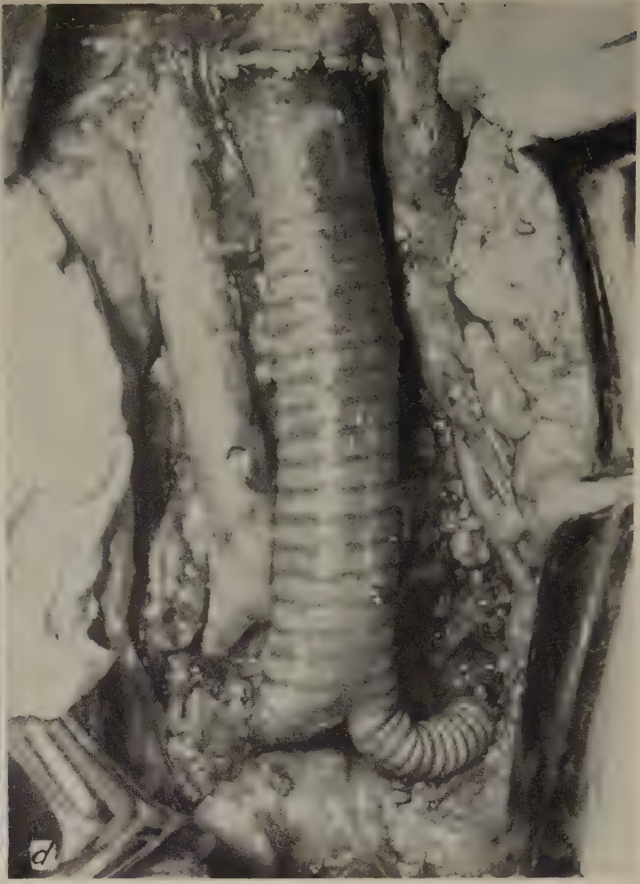
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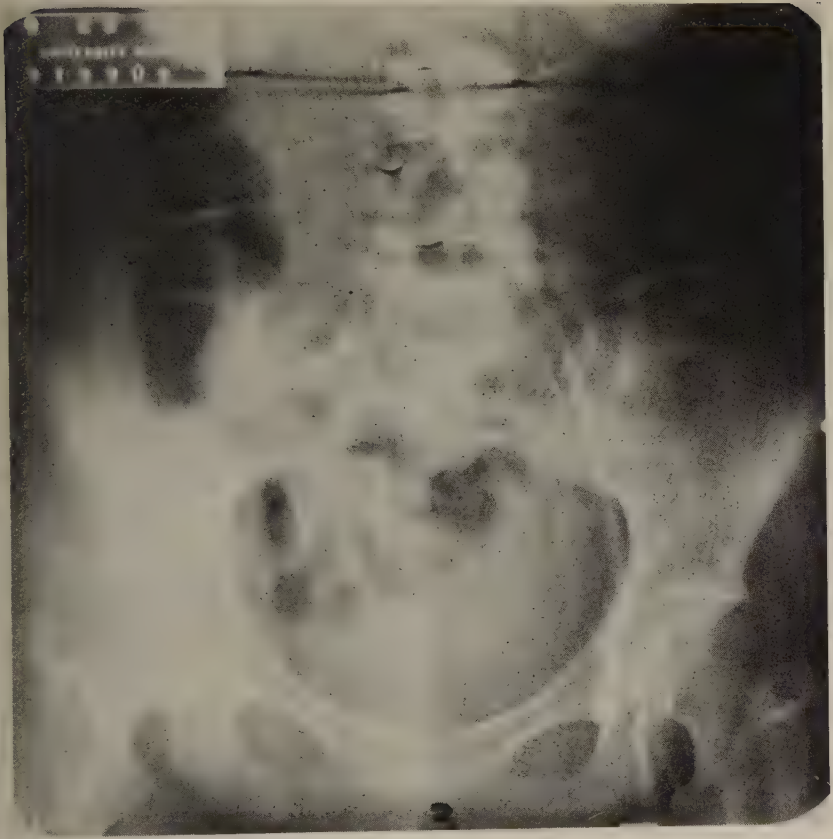


FIGURE 6. Thrombosis of right common iliac artery and irregularity of distal aorta. The left iliac is narrow, but patent (Case 6).

Case 8: femoral artery thrombosis. This 76-year-old male complained of intermittent claudication on the right for 2 months. The right femoral pulse was diminished. Labeled Renografin circulation study revealed an unusually prolonged arm to abdominal aorta interval of 24 sec. (FIGURE 8*a*). On the initial study, a single film was exposed for 5 sec., beginning 21 sec. after injection of the opaque material. This film was made too soon; contrast is seen in the renal arteries, but not in the distal aorta (FIGURE 8*b*). The following day a repeat study was done, and a film of the abdomen was exposed for 5 sec., beginning 25 sec. after injection of the contrast material; another film of the thighs was exposed for 5 sec., 29 sec. after injection. The iliac arteries are shown to be patent, and the right superficial femoral artery is blocked at its origin (FIGURE 8*c*, *d*).

Discussion

The ability to visualize the aorta and its major branches depends, of course, upon obtaining an adequate concentration of opaque material, and upon

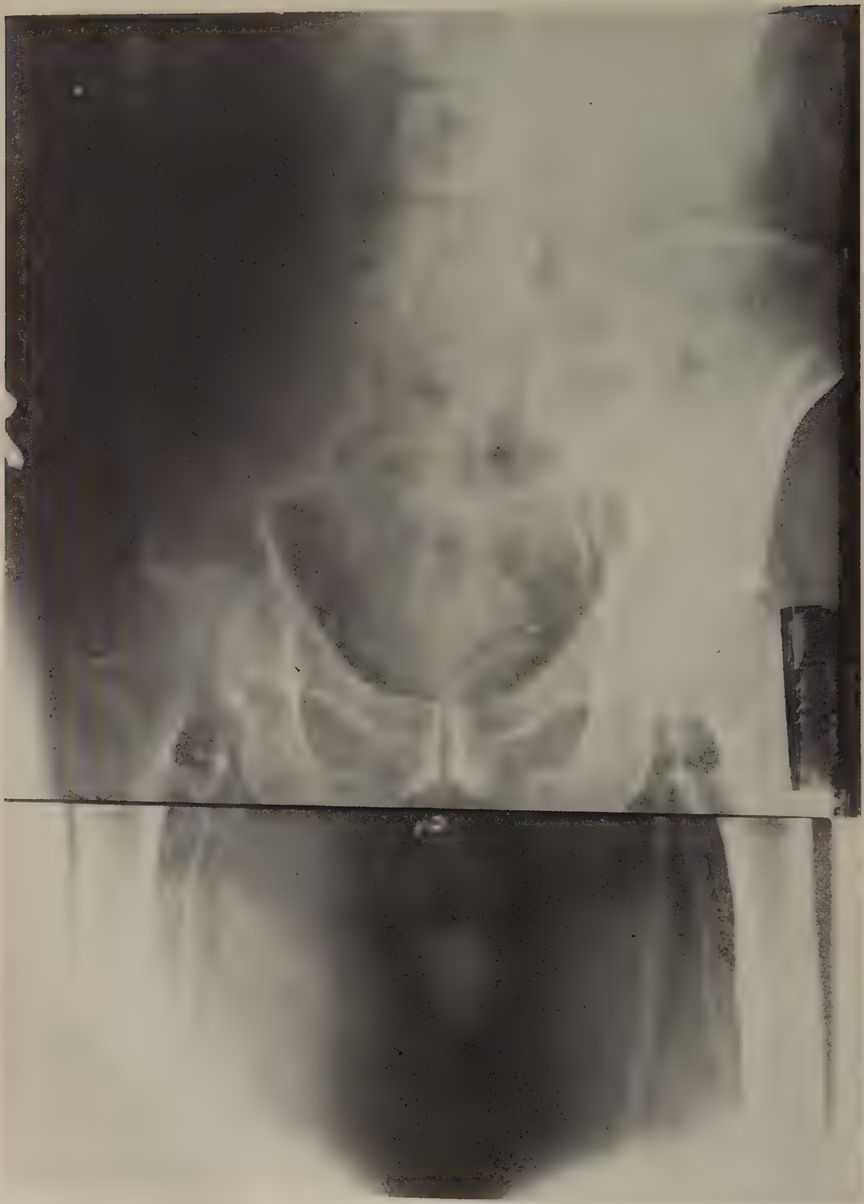


Figure 7. Thrombosis of right superficial femoral artery. The profunda has filled; the left superficial femoral is narrowed at its orifice, but patent. A single 6-sec. exposure was made, using two 14 × 17 casettes (Case 7).

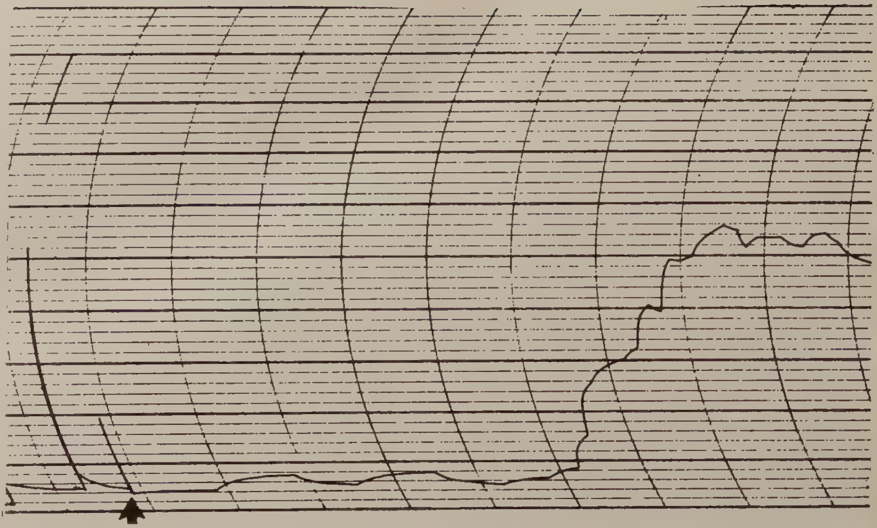
proper timing of the films. Utilizing a standard syringe and direct venepuncture with a large-bore needle, we have been unable to inject sufficient contrast material with adequate rapidity. The insertion of the small polyethylene catheter through a cut-down is a simple, rapid procedure, and running it a few inches up the vein prevents the vein from being forced off the edge of the catheter by the injection. The lever type of injector is ideally suited to this procedure, since it is possible to inject the entire 60- to 80-cc. dose in 1 to 2 sec., and the steel syringe precludes accidental breakage at time of injection. Initially, it was felt that, in elderly patients with poor cardiovascular systems, it might be necessary to advance the catheter from the arm to the superior vena cava, or perhaps directly into the right side of the heart in order to decrease dilution of the opaque material and achieve sufficient concentration in the aorta. However, this has not proved necessary. Intravenous aortograms have not been attempted in any patients in frank congestive failure, but several of the cases examined have had severe arteriosclerosis, hypertension, and large hearts.

The isotope timing is simple and accurate. It can be applied to any body area as long as the scintillation counter is held over a major vessel. It would be feasible to combine the I^{131}-labeled Renografin with the main injection of contrast material and have the X-ray exposure start automatically when sufficient radioactive pickup was obtained. However, observation of the isotope curve prior to the main injection of contrast medium has several advantages. With a very sharp slope to the appearance of isotopes over the aorta, one can be relatively certain that a good concentration of opaque material will be present and, if a rapid film changer is being used, fewer films need be taken. If the tracing over the aorta is more gradual in its rise, it is likely that flow is slower, and dilution may be occurring. Occlusive disease may, of course, also be present. In such cases, a larger volume of contrast material is injected, and films are exposed over a longer interval of time. In addition, the I^{131} Renografin mixture serves as an intravenous test dose of contrast.

The remarkably low toxicity of the sodium and methylglucamine diatrizoates permits the injection of large amounts of these substances into the vascular pool. The initial volumes used were 50 cc. of the 85 or 90 per cent concentration. This has gradually been increased to between 60 and 80 cc., without the occurrence of significant side effects. Animal studies are being performed in an effort to determine the toxic dose and margin of safety from a single massive injection. If these studies indicate its feasibility, the dose may be increased further. We appreciate dangers involved in large injections of contrast material, and have approached high dose levels with considerable caution. However, it is felt that the risk of massive intravenous injection is well justified in order to avoid blind puncture of the aorta (with the associated complications) and, where possible, to avoid the more difficult and complex direct arterial approaches.

Summary

A technique for the radiographic visualization of the abdominal aorta and iliac arteries and its clinical applications to a series of 41 patients is reported.



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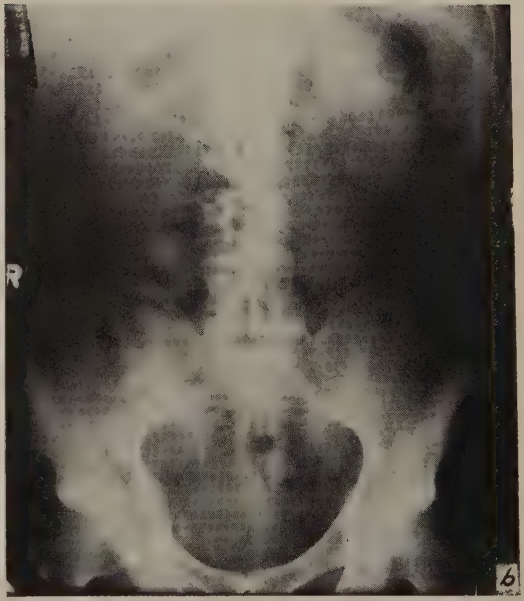

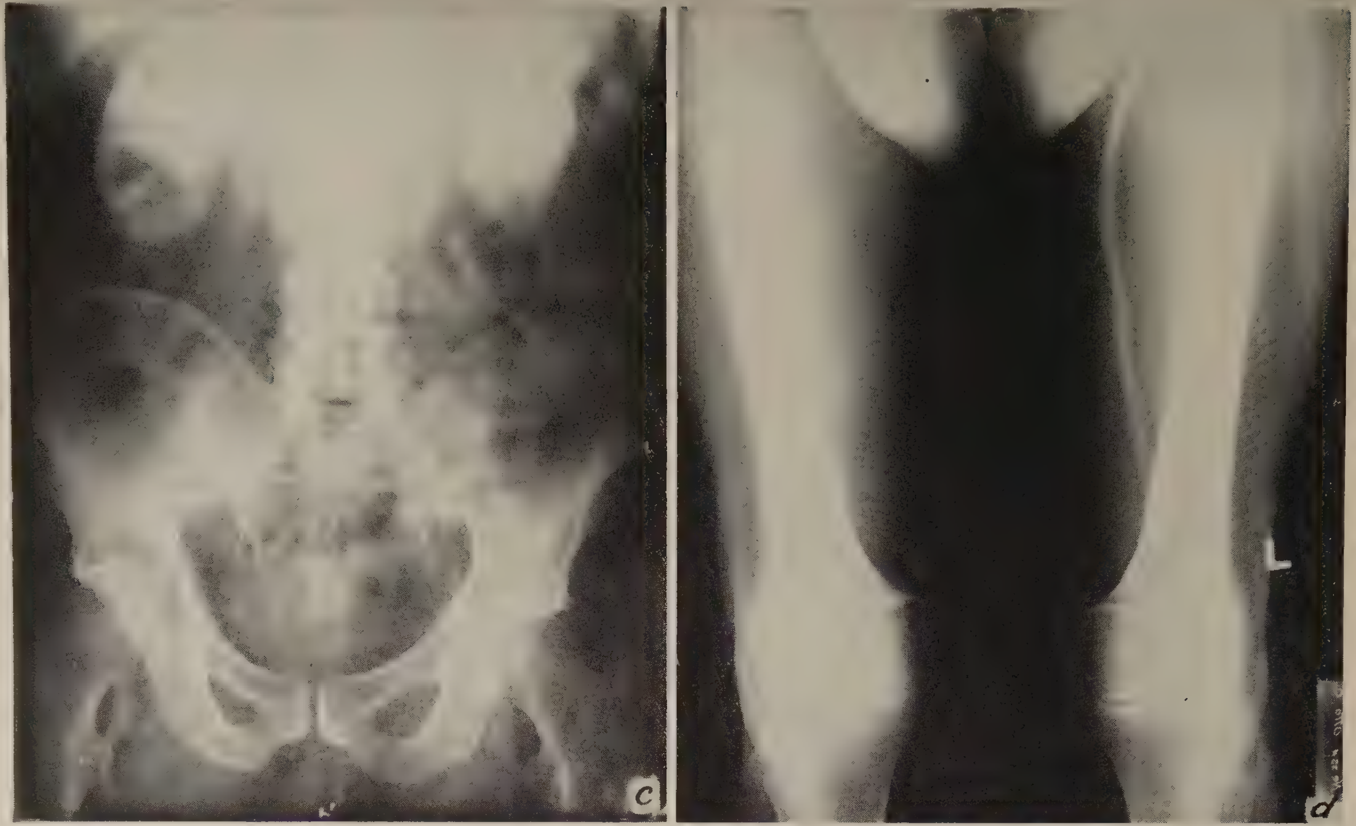

FIGURE 8. (*a*) I^{131}-Renografin tracing. A 24-sec. interval elapsed between injection and appearance of radioactivity at aorta. (*b*) Single 5-sec. exposure. Film was taken too soon and contrast shows in renal vessels, but not iliacs. (*c*) Repeat study. Exposure of film was begun 4 sec. later than in *b*. The iliacs are patent and no contrast appears in right superficial femoral. (*d*) Same case. A thrombosis of the right superficial femoral artery is shown. This 5-sec. exposure was started 4 sec. later than *c* (all Case 8).

The technique involves the use of a polyethylene venous catheter, radioactive iodine circulation-time studies using I^{131}-labeled Renografin, peripheral vascular occlusion, and a lever injector. The application of this technique to lesions of the great vessels and kidneys is illustrated. The advantages of this technique over translumbar aortography and other direct arterial approaches to the aorta have been discussed, as have some of the possibilities for the improvement of the method.

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HIGH CONCENTRATIONS OF DIATRIZOATE METHYLGLUCAMINE*

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The formulation of high-concentration sodium and methylglucamine diatrizoate compounds for use as intracardiac and intravascular opacifying agents appears to be a further significant step toward the objective of attaining a completely safe and satisfactory opacification medium.

Recent progress in the elaboration of procedures requiring direct introduction of relatively large amounts of undiluted radiopaque solutions into the cardiac chambers, the aorta, and larger arteries emphasizes the need for a continued search for ideal vaso-opacifying agents. Such procedures as selective catheter angiocardiography, catheter aortography, suprasternal thoracic aortography, cardiac ventriculography, and the several procedures designed for coronary arteriography require rapid boluslike injection of densely opacifying contrast media.

Our experience in the use of high-concentration sodium and methylglucamine diatrizoate agents forms the basis of this report.

The media we used were Cardiografin† in both 85 and 90.5 per cent concentrations, and Hypaque‡ in 85 and 90 per cent concentrations.

Cardiografin 85 per cent is a viscous fluid, containing 85 per cent of the methylglucamine salt of Renografin acid. It has an iodine content of 40 per cent. Its viscosity (Brookfield) at 25°C. is 35.5 cp.§

The 90.5 per cent solution of Cardiografin contains 30.5 per cent of the sodium salt and 60 per cent of the methylglucamine salt of Renografin acid. The iodine content is 46.5 per cent. Its viscosity (Brookfield) at 25°C. is 44 cp.§

Hypaque 85 per cent solution contains 28.33 per cent of the sodium salt and and 56.67 per cent of methylglucamine salt of diatrizoic acid. Its iodine content is 43.63 per cent, and its viscosity at 37°C. is 14.4 cp.§

The 90 per cent Hypaque solution contains 30 per cent of the sodium salt and 60 per cent of the methylglucamine salt of diatrizoic acid, and has an iodine content of 46.2 per cent. The viscosity at 37°C. is 20.2 cp.§

The Renografin acid of Cardiografin and the diatrizoic acid of Hypaque are structurally identical.§

In our use of these agents we have been concerned with problems of their rapid injection through the various catheters, needles, and tubing assemblies that we employ in our several cardiovascular opacification procedures. The high-concentration diatrizoate media are solutions of appreciable viscosity, and this influences their flow through small-bore tubing systems.

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† E. R. Squibb & Sons, New Brunswick, N. J.

‡ Winthrop Laboratories, Baltimore, Md.

§ Data supplied by manufacturer.

Flow rates of fluids through such systems are governed basically by Poiseuille's Law, which may be expressed as

$$Q - \frac{\pi P R^4}{8 \eta L}$$

where Q is the quantity flow per unit of time in cubic milliliters per second, P is the applied pressure in dynes per cubic centimeter, R is the radius of the tube in centimeters, L is the length of the tube in centimeters, and η is the coefficient of viscosity in poises. However, this expression must be applied with care, as it involves two basic assumptions: laminar flow and rigid tube walls. The first implies that the fluid motion is slow enough to avoid turbulence, which is reached at certain velocities and is dependent upon tube diameter and fluid density and viscosity; the latter assumes that distension of tubing causes changes in its radius and, in Poiseuille's Law, a small increase in R causes a large increase in Q.

It is important to recall that the viscosity of a fluid is influenced considerably by temperature. Thus, in clinical consideration of the flow rates of opaque media through systems such as catheters, small-bore plastic tubing, and needles, we are concerned with the pressure applied by the injection apparatus, the inside diameter of the system, the length of the system, and the viscosity of the media. In clinical practice, it is possible to vary only some of these factors. The size and length of the catheter or needle-tubing assembly may be fixed for the individual case by anatomical or technical considerations. Hence, consideration of all of the components of Poiseuille's Law may be important in achieving satisfactory radiopaque injection.

In selective angiocardiography, we have employed catheters of various lengths and gauges. These catheters have been of the thin-wall type (so-called Lehman Aortography Catheters*). The same catheters have been used for our catheter thoracic aortography studies.

For our cardiac ventriculography procedures (direct transthoracic needle puncture opacification of the left or right ventricle) and for our suprasternal thoracic aortography studies (suprasternal needle puncture opacification of the thoracic aorta), we utilize a 7-in. 17-gauge thin-wall needle of special design, and a plastic tubing and stopcock assembly† approximately 54 in. long.

The rapid injection of viscous opaque media through either the catheters or the needle-tubing assembly has presented certain difficulties. The diatrizoate sodium and methylglucamine compounds cannot be injected by manual syringe pressure, either through the catheters we regularly use or through the needle-tubing assembly, in a sufficiently short time and in sufficient amounts to effect satisfactory studies. It has been necessary to utilize some type of mechanical or pneumatic injector to obtain sufficient injection pressure.

For the majority of our clinical studies, we have employed a mechanical

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* United States Catheter Corporation, Glens Falls, N. Y.

† George P. Pilling and Sons, Philadelphia, Pa.

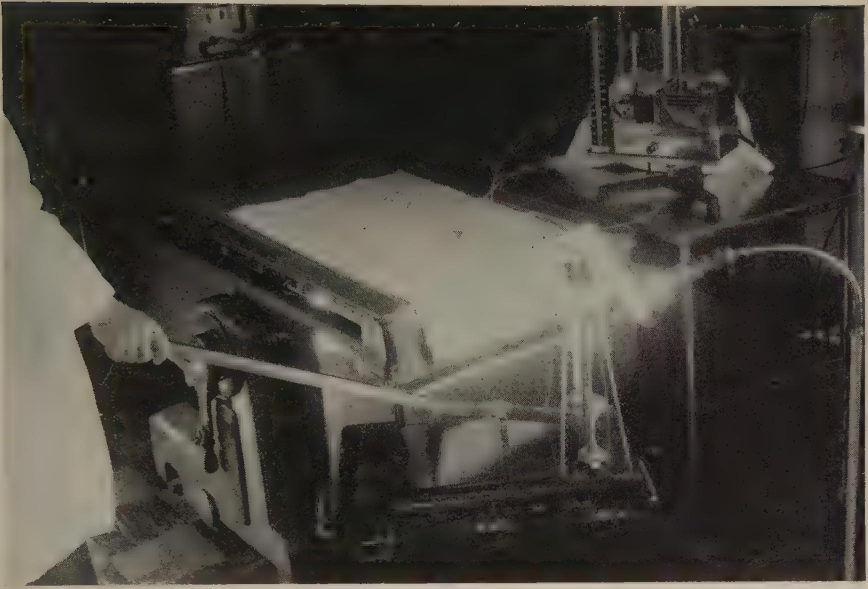

FIGURE 1. Mechanical pressure injector.

injection apparatus of our own design (FIGURE 1),* which utilizes the principle of a simple lever. With this apparatus we use a glass syringe of 50-cc. capacity; this syringe is also of special design.† Continuous heating of the syringe and its content of opaque medium is maintained by directing the rays of a heat lamp toward the filled syringe, as shown in FIGURE 1.

For some of our clinical studies and the majority of our animal experimental studies, a Gidlund‡ injection apparatus with a pneumatically driven piston has been used (FIGURE 2). This apparatus maintains a thermostatically controlled temperature. The maximal injection pressure attained by the Gidlund unit is 10 kg./sq. cm.; the maximal injection pressure with our mechanical injector, as we employ it, is 8 kg./sq. cm.

Flow-rate curves for 6-, 7-, 8-, and 10-gauge catheters were obtained using the Gidlund injector and aortography catheters 100 cm. long, with closed ends, and with 4 side holes located in the distal 14 mm. of the catheter; these were connected to the pressure injector by a 100-cm. length of plastic tubing. The radiopaque medium used for this study was Cardiografin 85 per cent, kept at a constantly regulated temperature of 45°C. The curves of the flow rates, in milliliters per second and at various injection pressures for the several catheters, are illustrated in FIGURE 3.

The influence of temperature of the medium on flow rates is illustrated in

* Franklin X-ray Company, Philadelphia, Pa.
† Becton-Dickinson and Company, Rutherford, N. J.
‡ Schick X-ray Company, Chicago, Ill.

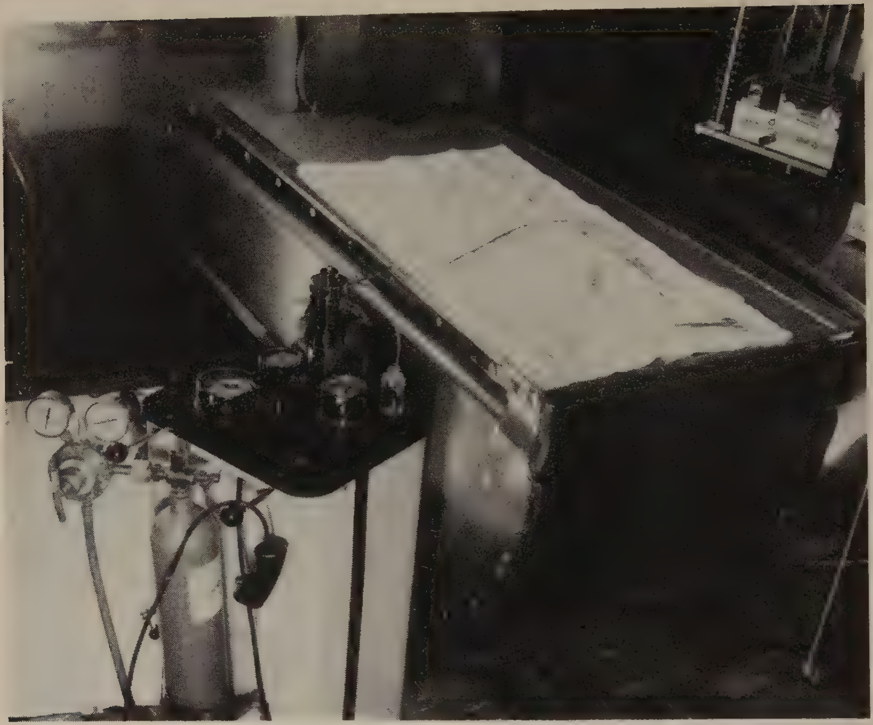

FIGURE 2. Gidlund pressure injector.

FIGURE 4. In this study, both 85 and 90.5 per cent Cardiografin solutions were used in amounts of 20 cc. at various temperatures and at various injection pressures. We utilized a No. 7 aortography catheter with closed end and distal side holes, 100 cm. long and connected to the injection apparatus by a 135-cm. plastic tubing and stopcock assembly. It is obvious from these studies that preheating of high-concentration radiopaque media of the diatrizoate sodium and methylglucamine type facilitates their rapid injection through catheters. This applies also to injection through needle tubing assemblies.

In clinical usage it has been our practice to heat the medium to a temperature of at least 38°C. On numerous occasions, in clinical practice, we have injected the solution at 45°C. In animal studies, the temperature of the injected medium has been as high as 60°C. There have been no observable sequelae related to the injection of radiopaque medium at the temperatures we have used. It is our belief, admittedly without experimental confirmation, that a 2-sec. injection of 50 cc. of radiopaque medium into a cardiac chamber or the aorta of man, at a temperature as high as 60°C., produces no local tissue damage, local physiological aberration, or generalized systemic effect related to the temperature of the opaque medium. It is reasonable to presume that there is such rapid heat dispersion and dissipation in an accelerated column of medium that local tissue damage is quite improbable.

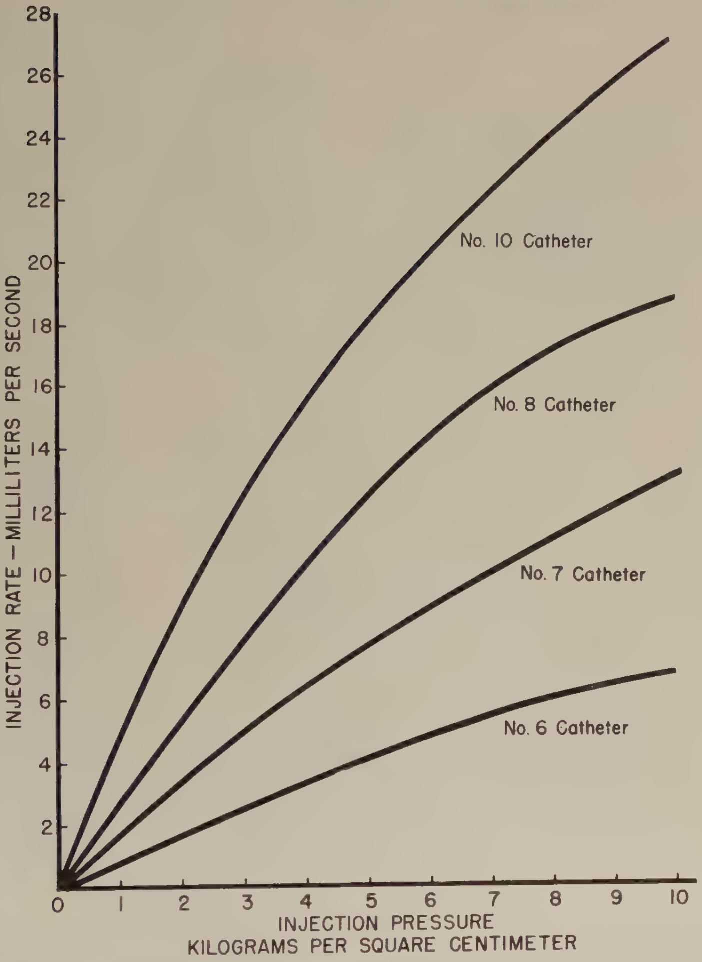

Figure 3. Flow rates through aortography catheters at various injection pressures.

That rapid injection is a necessity is well known to all practitioners of angiocardiography and related procedures. Satisfactory opacification studies in such procedures require the delivery of the bolus of contrast material in a relatively short period, usually considered as no longer than 3 sec. A 2-sec. injection would be ideal.

When opacifying media of the viscosity of diatrizoate sodium and methylglucamine compounds are adapted to procedures that require injection through catheters or needle-tubing assemblies in amounts such as are employed for adults (20 to 50 cc.), some type of pressure injector is a requisite. It has been our experience that the gain in injection rate resulting from heating the solution is frequently necessary to achieve sufficiently rapid delivery of the opaque substance.

The radiopacity of both the 85 and 90 per cent concentrations of the diatrizoate compounds is sufficient for good-quality cardiovascular opacification. In our clinical practice we have attempted to determine whether we could distinguish between the degrees of visualization produced by the 85 and the 90 per cent solutions; our observations in this regard have been negative.

In a further attempt to decide whether there was a distinguishable difference in the opacity produced by the 2 concentrations, we filled ordinary soda straws with the 2 concentrations of both Cardiografin and Hypaque, and inserted these straws into a Presdwood phantom of varying thickness, with a maximum of 12 cm. Radiographs were made of the phantom and its straw inserts at 60, 75, 90, and 105 kv., with adjustment of the milliampere seconds to obtain comparable film exposures. Additional studies were performed with the straws

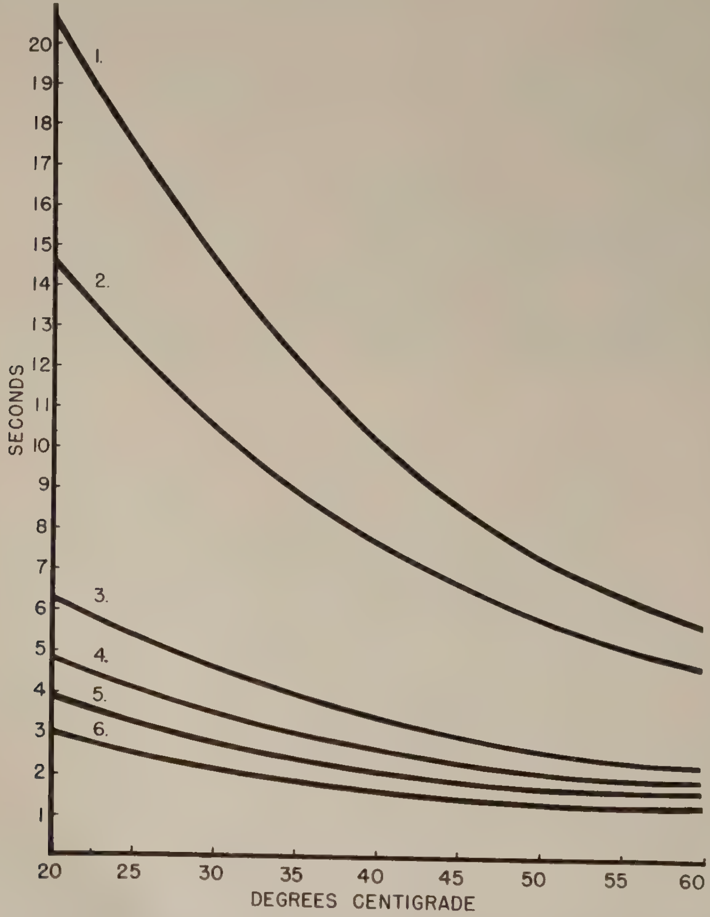

FIGURE 4. Influence of temperature on flow rate through aortography catheter. Curves are for concentrations of Cardiografin, as follows: (1) 90.5 per cent, 2 kg./sq. cm.; (2) 85 per cent, 2 kg./sq. cm.; (3) 90.5 per cent, 6 kg./sq. cm.; (4) 85 per cent, 6 kg./sq. cm.; (5) 90.5 per cent, 10 kg./sq. cm.; and (6) 85 per cent, 10 kg./sq. cm.

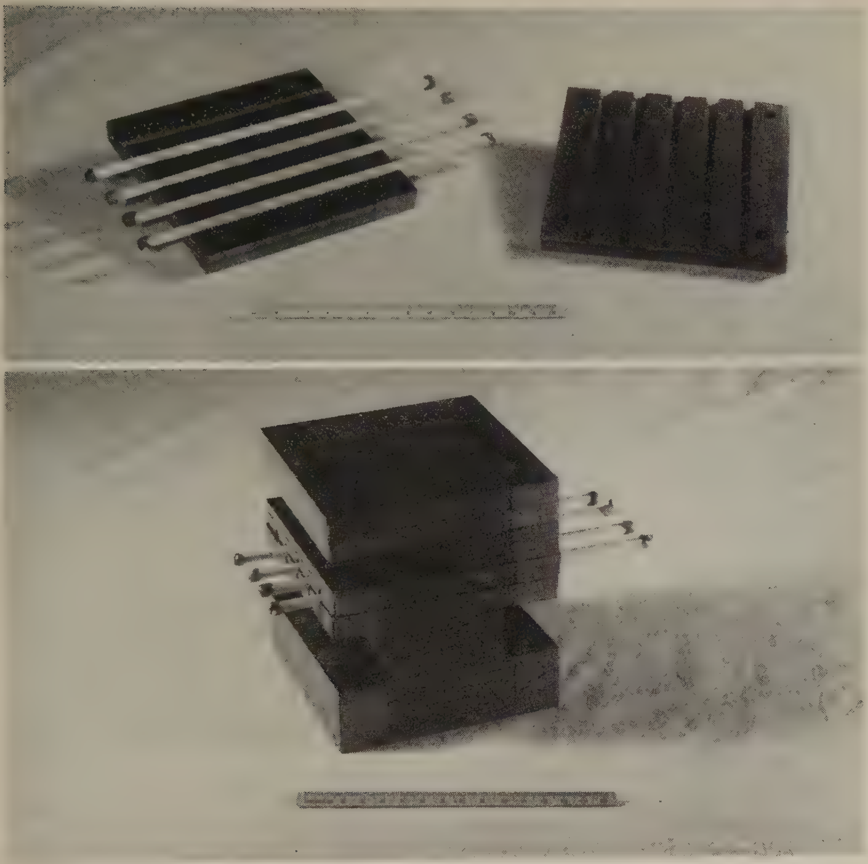

Figure 5. Presdwood phantoms and straws filled with opaque media. (a) Phantom with 12-mm. thickness. (b) Phantom of varying thickness, with a maximum of 12 cm.

placed upon a Presdwood phantom of 12-mm. thickness. This experiment demonstrated that there was no optically distinguishable difference in the radiopacity of the 85 and 90 per cent media, nor was there any apparent difference in the radiopacity of Cardiografin as compared to Hypaque for the high-concentration solutions. Figure 5 shows the Presdwood phantoms, and figures 6 and 7 show the films obtained in these studies. In a further step, we placed the thin (12 mm.) phantom with filled straws upon the chest of a patient, in a position overlying the heart, and obtained film studies at various exposure factors. In this test, also, we were unable to distinguish any difference between the 85 and 90 per cent concentrations.

The toxicity or lack of toxicity of the high-concentration sodium and methylglucamine diatrizoate compounds, and the local and systemic reactions to these agents are of commanding interest. While we have not engaged in studies of

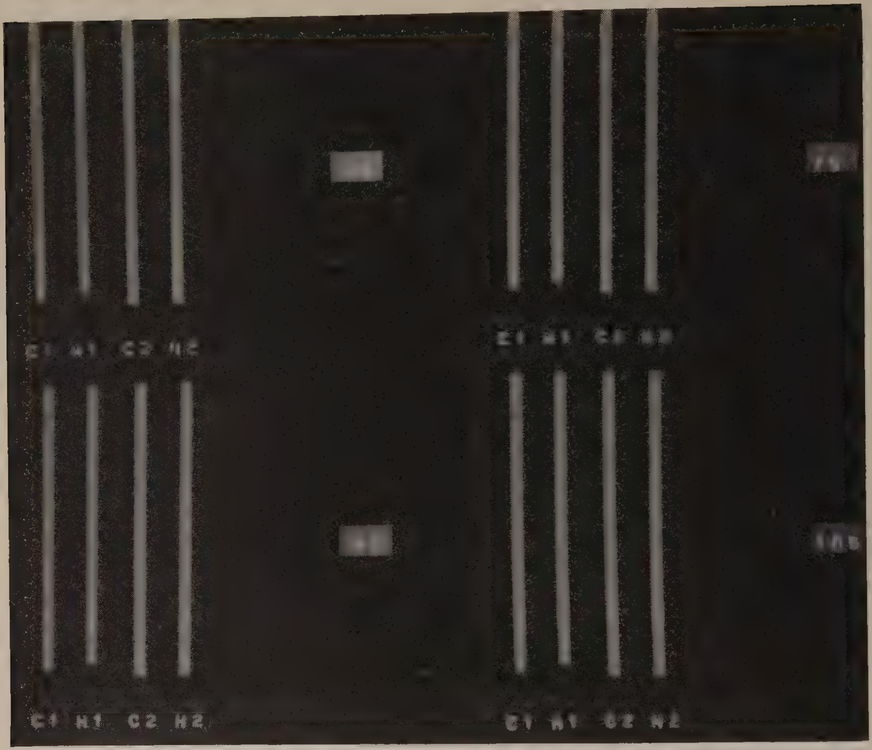

FIGURE 6. Radiographs of opaque-filled straws on 12-mm. phantom made at 60, 75, 90 and 105 kv. C 1 represents Cardiografin 85 per cent; H 1, Hypaque 85 per cent; C 2, Cardiografin 90.5 per cent; and H 2, Hypaque 90 per cent.

the lethal doses of these media, we have observed that they are well tolerated by experimental animals in doses required for excellent cardiovascular opacification.

In certain coronary arteriographic investigations in dogs, we have made multiple injections of 10-cc. doses of these media through a catheter introduced into the ascending aorta and positioned with its tip at the level of the aortic sinuses. Each 10-cc. injection was made in 2 sec. or less, and we have repeatedly injected as many as 12 such doses in 10-kg. dogs throughout an investigation of several hours. The dogs have regularly survived the total dose of 120 cc. without apparent sequelae. This is in distinct contrast to our experience with a 70 per cent iodopyracet compound, where doses of the same magnitude administered under identical conditions were usually lethal.

In clinical studies on humans we have been impressed with the relative absence of severe or serious systemic reactions to these high-concentration diatrizoate media in the doses employed. While we have not followed a distinct formula of dosage relative to body weight of patient in our selective catheter angiocardiographic studies, we have injected a dose varying from 25

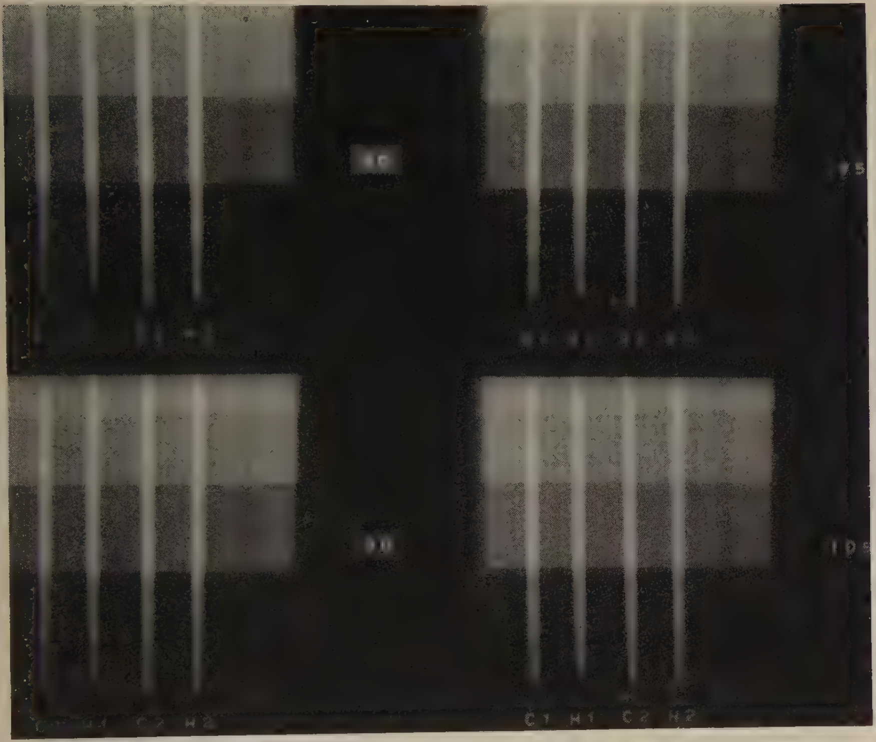

FIGURE 7. Radiographs of opaque-filled straws in a phantom of varying thickness made at 60, 75, 90, and 105 kv. C 1 represents Cardiografin 85 per cent; H 1, Hypaque 85 per cent; C 2, Cardiografin 90.5 per cent; and H 2, Hypaque 90 per cent.

to 50 cc. in the average adult. In the majority of our catheter thoracic aortographies, coronary arteriographies, cardiac ventriculographies, and suprasternal thoracic aortographies, the injected dose has been 35 cc. for an average adult. This dose has been delivered in from 1.5 to 3.0 sec.; in the majority, the injection was made in 2.0 sec.

In these studies, the opacifying agent is delivered into either the left ventricle (cardiac ventriculography-left) or into the ascending aorta in other procedures. Dense opacification of the brachiocephalic vessels taking origin from the aortic arch is regularly observed. Relatively high concentrations of opacifying media enter the carotid arteries, since we have made no attempt to compress them during the injection. It is noteworthy that we have observed no evidence of cerebral injury, damage, or dysfunction as a result of these concentrated radiopaque media entering the cerebral circulation.

Almost all patients receiving the dose of medium that we have injected experience some systemic reaction. In the great majority this has been a subjective sense of heat, with occasional observable flushing. This is usually first noted in the face, neck, and thorax. A fair percentage of patients observe that the sensation of heat spreads rapidly to the head, arms, abdomen, pelvis, and lower extremities. This sensation is usually of only moderate degree and regularly of short duration, rarely lasting more than several minutes. Headache, which may be generalized or frontal in location, varying in degree from slight to moderate and occasionally rather severe, has been a not infrequent complaint. It is generally of short duration, usually about 5 min. Occasionally nausea and, rarely, vomiting have been observed. There have been a few occasions of momentary slight syncope.

Hypersensitivity or allergic reactions to the high-concentration diatrizoate opaques have been comparatively rare. We have experienced no definite allergic reactions other than 3 instances of mild urticaria. In these 3 cases, hives were noted on the face and neck in 2, and also on the arms in the third patient. In no instance were they very extensive or of alarming degree and, in each case, response to antihistamines was satisfactory.

We have encountered no shocklike state that we could not attribute to other features of the procedure, other than 11 occasions of momentary faintness or momentary slight syncope. There was 1 case of slight tonic convulsion immediately after injection of 35 cc. of 90 per cent opaque for cardiac ventriculography.

In general, the systemic reactions have been of lesser degree than those noted for similar procedures in which iodopyracet and acetrizoate sodium radiopaque agents have been used.

The reactions recorded for the several procedures in which both the 85 and 90 to 90.5 per cent sodium and methylglucamine radiopaques were used are summarized in TABLE 1. The examinations listed in the table were all performed in patients 9 years of age and older. Infants and young children were excluded on the basis that they were either too young to supply valid information on subjective reactions, or were under general anesthesia during the examination. Thus, 1 cardiac ventriculography, 21 angiocardiographies, and 4 catheter thoracic aortographies have been excluded. In none of these was there any perceptible reaction to the high-concentration diatrizoate radiopaque agents.

It is our regular practice to monitor the several opacification procedures previously mentioned by continuous electrocardiographic study. Customarily, we employed a standard Lead 2 for our recording. Admittedly, certain electrocardiographic changes incident to injection of the medium may not be detected with a single Lead 2 observation; however, our particular procedure arrangement does not permit simultaneous recording of multiple leads. The Lead 2 studies do indicate that certain changes in rate and, on occasion, of rhythm occur with some frequency during the rapid injection of opaque medium directly into the left ventricle (cardiac ventriculography-left), or directly into the ascending aorta (catheter thoracic aortography and suprasternal thoracic aortography). In considering the cause of such electrocardiographic change, it is important to attempt to determine whether the changes are due to the direct physical impact of a jet of opaque solution issuing from the catheter or needle openings impinging upon the endocardium or endothelium, or to the

TABLE 1

Procedure	Concentration of opaque medium (percentages)	Dose range (cc.)	Usual adult dose (cc.)	No. of examinations	Quality of opacification				Incidence of reactions																
									Heat			Flushing			Headache			Nausea			Vomiting				
					Excellent	Good	Fair	Poor	Slight	Moderate	Severe	Slight	Moderate	Severe	Slight	Moderate	Severe	Slight	Moderate	Severe	Slight	Moderate	Severe	Faintness	Urticaria
Cardiac ventriculography* (166 examinations)	90–90.5	15–55	35	149	65	69	12	3	43	99	2	6	10	—	17	19	8	9	9	—	3	1	—	6	2
	85	25–50	35	17	4	8	5	—	4	13	—	—	2	—	3	3	2	1	—	—	—	—	—	1	—
Suprasternal thoracic aortography (91 examinations)	90–90.5	20–55	35	82	29	40	10	3	7	71	2	6	1	1	9	8	1	5	3	—	3	1	—	3	1
	85	25–50	35	9	3	5	1	—	1	8	—	—	1	—	1	1	—	2	—	—	—	—	—	—	—
Selective angiocardiography (21 examinations)	90–90.5	10–55	50	18	7	10	—	—	2	15	—	2	1	—	—	—	—	—	—	—	—	—	—	1	—
	85	30–50	50	3	2	1	—	—	—	3	—	—	1	—	1	—	—	—	—	—	—	—	—	—	—
Catheter thoracic aortography (9 examinations)	90–90.5	25–38	35	5	2	3	—	—	2	3	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
	85	35–55	35	4	1	1	—	—	—	4	—	—	—	—	—	1	—	1	—	—	—	—	—	—	—

* One case of slight tonic convulsion.

effect of physiological-pharmacological aberrations caused by properties of the opaque medium.

In our rather limited number of selective (catheter) angiocardiographies monitored by electrocardiographic control and employing the diatrizoate agents we have observed instances of short periods of bradycardia followed by supraventricular tachycardia. These have not been appreciably different from a limited number of observations made with media other than the diatrizoate compounds.

The electrocardiographic observations made during direct transthoracic needle puncture opacification of the left (or right) ventricle (cardiac ventriculography) have been published by Lehman *et al.*[1] In this report of our first 77 such studies in 60 patients, a brand of iodopyracet (Diodrast 70 per cent) was injected. We now have experience with 166 additional cardiac ventriculographies in which either Cardiografin or Hypaque in 85 or 90 per cent concentrations was used. We are tabulating for publication our experiences with these additional cases. While this tabulation is not yet complete, we are impressed by the fact that the electrocardiographic changes related to the physiological-pharmacological response to the diatrizoate agents do not differ greatly from those observed with Diodrast 70 per cent. Briefly, these may be summarized as follows: In somewhat less than one half the patients, a short period of moderate bradycardia occurred immediately upon completion of the opaque injection. This usually was followed by a moderate supraventricular tachycardia. Occasionally there were *S-T* segment and *T*-wave changes that were of a transitory nature. On rare occasions there has been a momentary change in cardiac rhythm.

Our complete experience with suprasternal needle puncture opacification of the ascending aorta (suprasternal thoracic aortography)[2] is also being prepared for publication. Final analysis of the electrocardiographic changes incident to introduction of high-concentration radiopaques by this procedure is not yet complete. It can be indicated, however, that direct rapid deposit of the radiopaque medium into the region of the aortic sinuses and coronary ostia is prone to produce transitory change in the *S-T* segment and *T*-waves. This is to be expected since, by this procedure, there is greater likelihood of the entrance of considerable concentrated opaque solution into the coronary arterial system. It is our belief that such *S-T* changes reflect momentary myocardial ischemia, and that it is doubtful that there are other significant pharmacological effects on the coronary arterial system or the myocardium. When these changes have been observed, they have been of very short duration.

What has been said for the electrocardiographic changes as related to suprasternal thoracic aortography applies equally to catheter thoracic aortography. The electrocardiographic observations with relation to opaque medium injection in this procedure have, in large measure, paralleled those of the suprasternal needle injection technique.

Finally, we have been impressed by the fact that, from the standpoint of general systemic reactions, local cerebral toxicity or damage, and coronary or myocardial effects, the high-concentration sodium and methylglucamine diatrizoate radiopaque solutions are acceptable, reliable, and relatively safe agents for the opacification procedures mentioned in this report.

Summary

High concentrations of diatrizoate sodium and methylglucamine radiopaque compounds are satisfactory media for angiocardiography, catheter thoracic aortography, suprasternal thoracic aortography, coronary arteriography, and cardiac ventriculography.

These media have appreciable viscosity, and the problems of their rapid injection through catheters and small-bore tubing-needle systems are discussed.

The systemic reactions incident to the use of these media are tabulated and discussed.

Certain comparisons of the 85 and 90 to 90.5 per cent concentrations of these media are described. In clinical application and in certain radiopacity studies we have been unable to determine appreciable differences between these concentrations.

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LARGE-VOLUME MYELOGRAPHY

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The introduction of Pantopaque for myelography in 1944 by Ramsey and Strain[1] marked the beginning of modern myelography. Dandy[2] is credited with the introduction in 1919 of the technique of myelography that uses air as a contrast medium for visualization of spinal cord tumors. In 1922 Sicard and Forestier[3] introduced iodized poppy-seed oil as a myelographic contrast medium. From 1922 to 1944 no significant improvements in this procedure were suggested. During this long interval, relatively few examinations were done because of the extreme difficulty of interpreting air myelograms, the difficulty in removing iodized poppy-seed oil, and the lack of absorption of the oil when left in the canal.

Pantopaque, a mixture of ethyl esters of isomeric iodophenylundecylic acids, has been reported to be absorbed from the spinal fluid at the rate of 1 cc. per year.[4] This absorption rate, although low, leaves room for considerable improvement. The insignificant absorption rate, in addition to the lack of local and systemic reactions, has led to the wide acceptance of this radiopaque agent.

Early workers[1] advocated the use of 3 to 5 cc. of the medium. Grayson and Black[5] first reported on large-volume myelography in 1949, using 12 cc. They reported a surgically proved diagnostic accuracy of 95 per cent. We have seen no reason in the intervening 9 years to question this degree of accuracy. Since 1947, using the large-volume technique, we have done over 3000 myelograms without untoward clinical effects. We believe this procedure to be safe in all respects, even in the event of technical accidents. The excellent report on this technique in 1953 by Mallis *et al.*[6] supported our original report and clarified some of the technical concepts.

It is my purpose here to illustrate the average myelogram produced by this method and to describe some of the technical misadventures.

Method

The patient is premedicated with a barbiturate only. An 18-gauge spinal needle is introduced into the spinal canal at a level above the site of the expected pathology; meticulous care is used to place the needle exactly in the midline. Spinal fluid (10 cc.) is removed for laboratory studies. Dye (1 cc.) is introduced with the patient in the prone position. The position of the needle and the ability of the dye to flow freely in the spinal canal is then checked with an "image amplifier," the table being tilted both cephalad and caudad. Additional dye is then introduced until 12 cc. has been added. The X-ray table is tilted upright and, with the patient standing, the level of the dye is checked. If the third, fourth, and fifth lumbar interspaces are covered with the oil column, no additional dye is added; however, in the event the column of dye does not extend to this level, more dye is introduced. The total quantity is not a material consideration. Sufficient dye is used to cover at least the third, fourth,

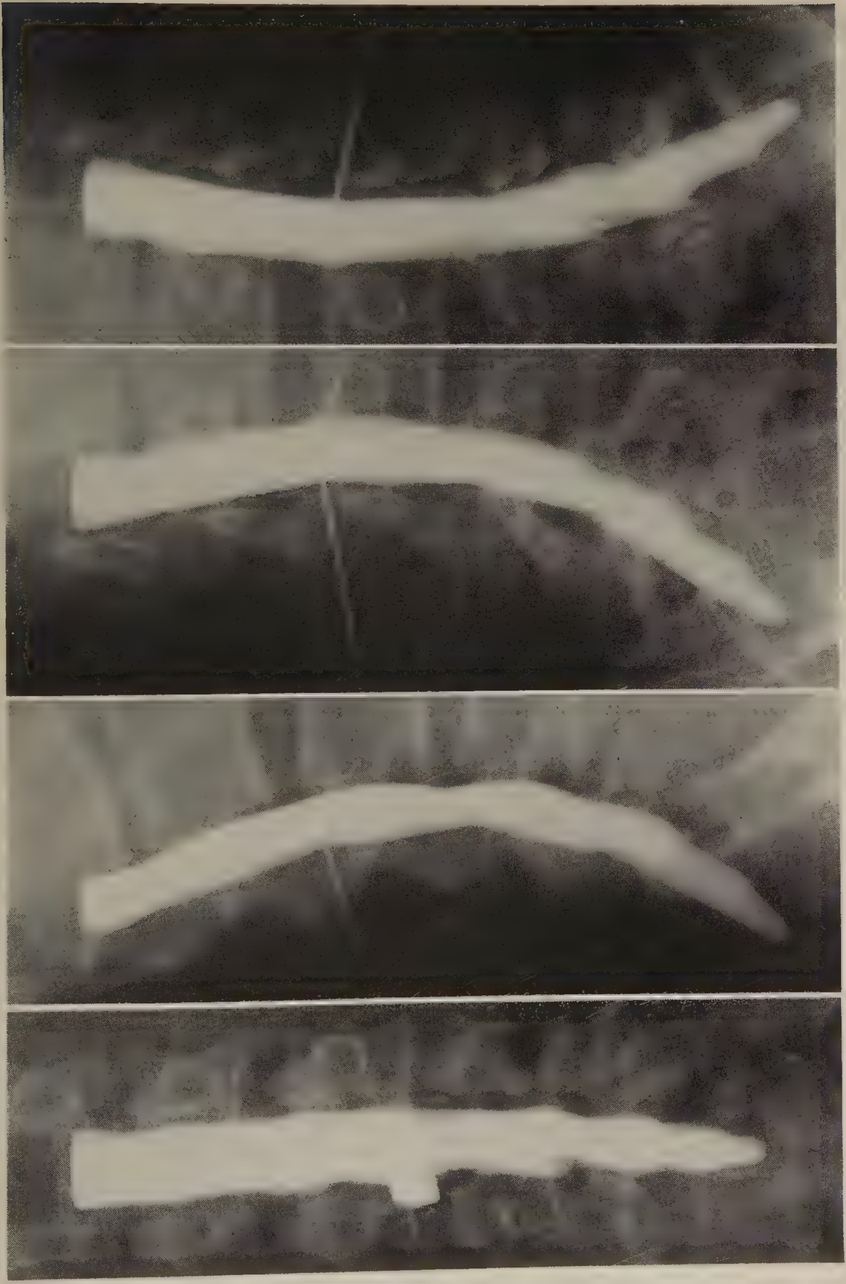

Figure 1. Routine views used in all cases; a normal myelogram.

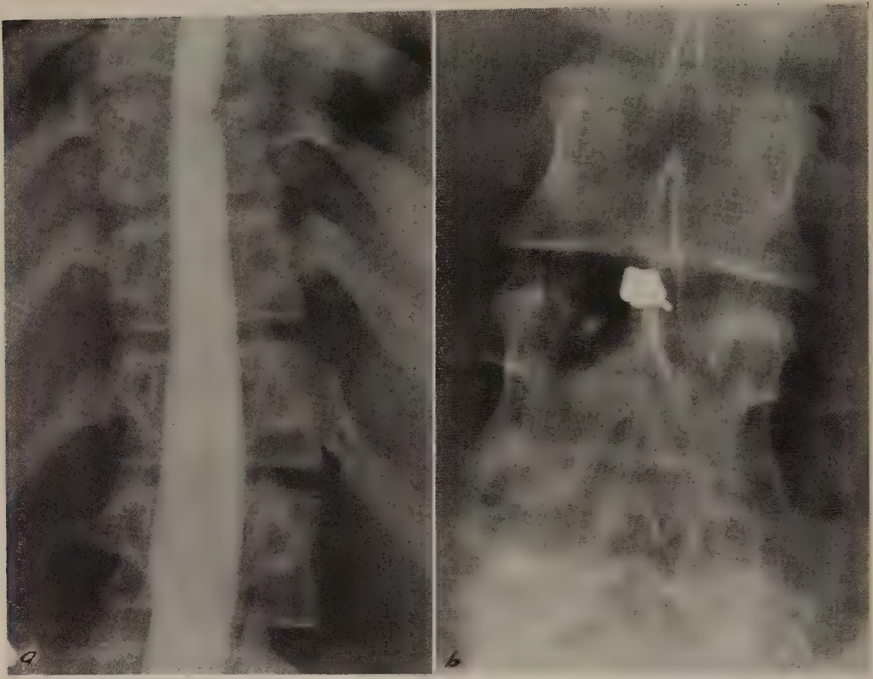

FIGURE 2. (*a*) Fluorogram of upper lumbar and lower dorsal areas. (*b*) Fluorogram of canal after removal of the radiopaque.

and fifth intervertebral spaces. Routine upright roentgenograms are then taken on 14- × 17-in. films in P-A, lateral, and left and right oblique projections (FIGURE 1). Under fluoroscopic control, the dye is then run upward by tilting the table appropriately. The remaining lumbar interspaces are checked and fluorograms are made (FIGURE 2*a*). The oil column is always carried into the mid-dorsal region.

Films are then checked for technique and, if satisfactory, the dye is removed by aspiration (FIGURE 2). No difficulty is encountered until the last 0.5 cc. remains. It is usually necessary to center this last drop under the tip of the needle by tilting the table; this is accomplished with an image amplifier or with screen fluoroscopy.

Findings

For the purpose of this study, 297 consecutive cases were reviewed from a total experience of over 3000 myelograms. The volume of radiopaque agent utilized varies considerably with the caliber of the spinal canal and the level of the suspected pathology. The frequency with which various quantities of dye were used is shown in FIGURE 3.

The smallest volume of dye used was 3 cc. (7 cases), and the most frequently used volume was 18 cc. (107 patients); 30 cc. was used in 36 cases and, in 2 instances, as much as 60 cc. was injected.

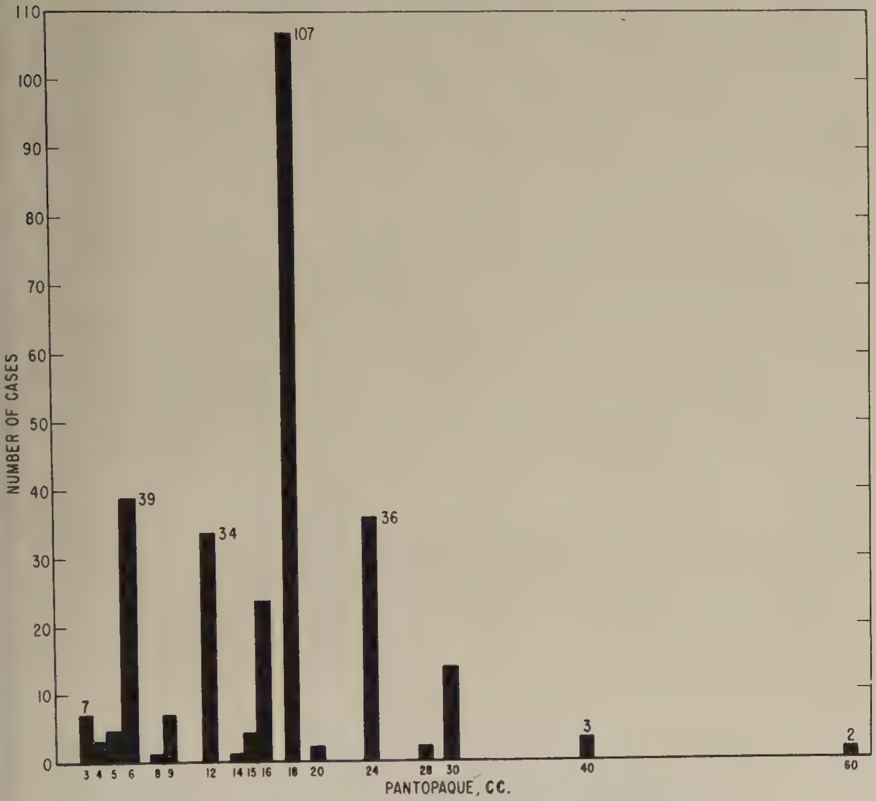

FIGURE 3. Frequency of use of various quantities of Pantopaque.

TABLE 1
SUMMARY OF RESULTS IN 297 CASES

Total cases	297
Male	182
Female	115
Normal	114
Abnormal	183
Disk	135
Single	124
Double	11
Ridge deformity	69
Single	44
Multiple	25
Spur defect	6
Block	11
Disk	5
Tumor	4
Congenital bone anomaly	1
Postsurgical	1
Technical deviations	14
Extradural injection	12
Direct vascular injection	2

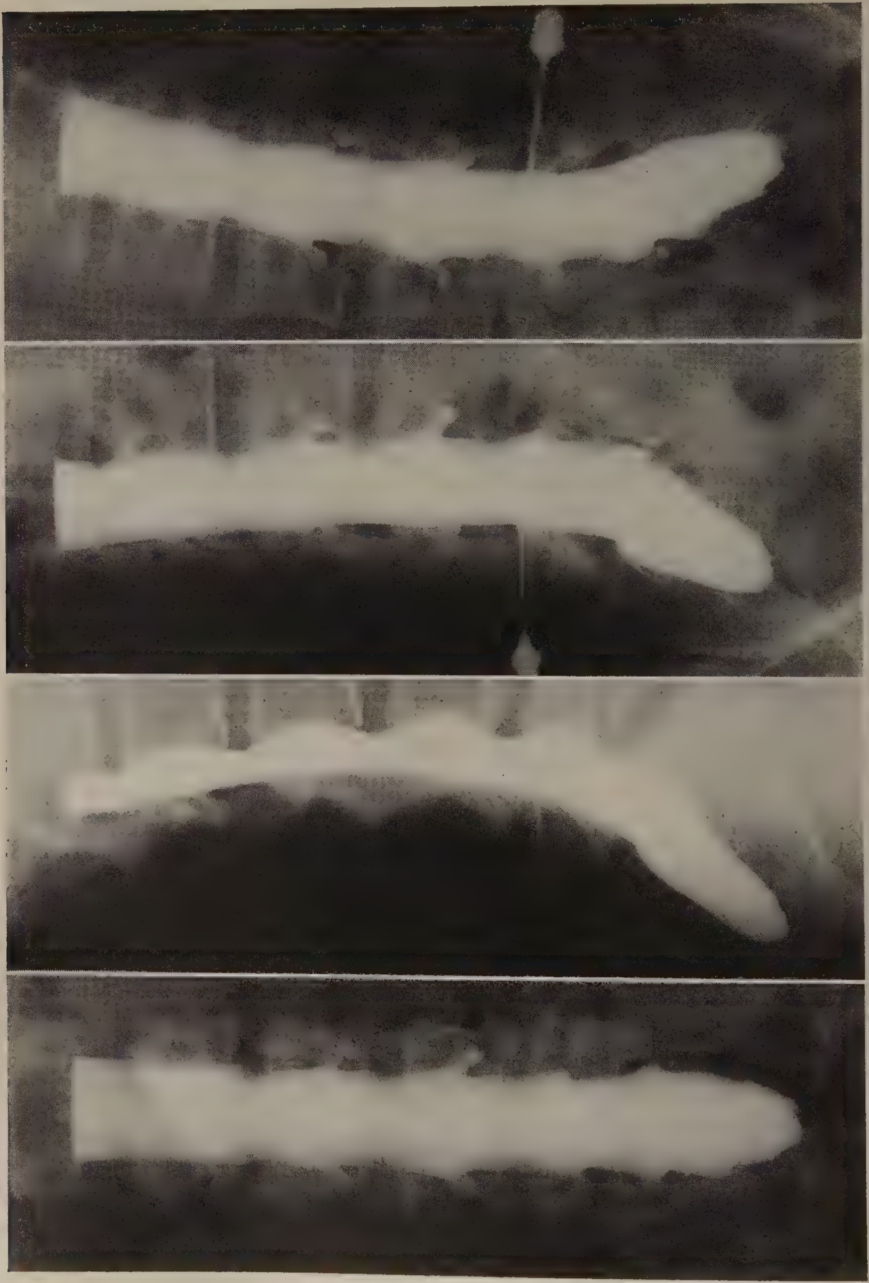

FIGURE 4 Ridge deformities seen in lateral view only; remaining projections reveal no filling defects

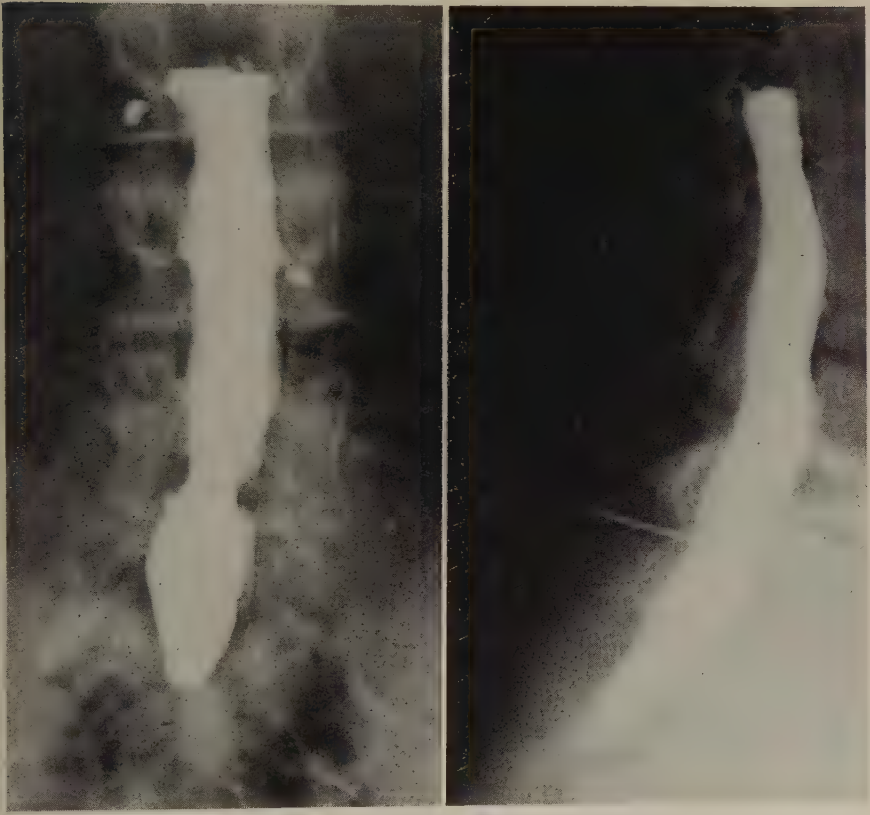

FIGURE 5. Note the filling defect in the oil column on right at the fourth interspace. Lateral projection shows this to be due to a bone spur.

There were 182 males and 115 females in this group (TABLE 1). Normal myelograms were found in 114 cases, representing almost 40 per cent of the total. In the abnormal group there were 69 cases in which "ridge deformities" were noted; of these, 44 were single and 25 were multiple. In 6 cases defects in the oil column were produced by hypertrophic bone spurs; in 11, complete block of the spinal canal was found. Of these, 5 were caused by herniated intervertebral disks, 4 by tumor, 1 by a congenital bone anomaly and 1 by a postsurgical deformity.

In this group there were 14 instances of technical deviations from the accepted normal procedure; in 2 of these, there were direct vascular injections of the dye and, in 12, various quantities of oil were injected intradurally.

The typical ridge deformities in the abnormal group are shown in FIGURE 4; note the symmetry of the defect or defects and the slight settling or narrowing of the intervertebral spaces at the level of involvement. The defects are due to bulging of the annular ligaments and, possibly, to some relaxation of the liga-

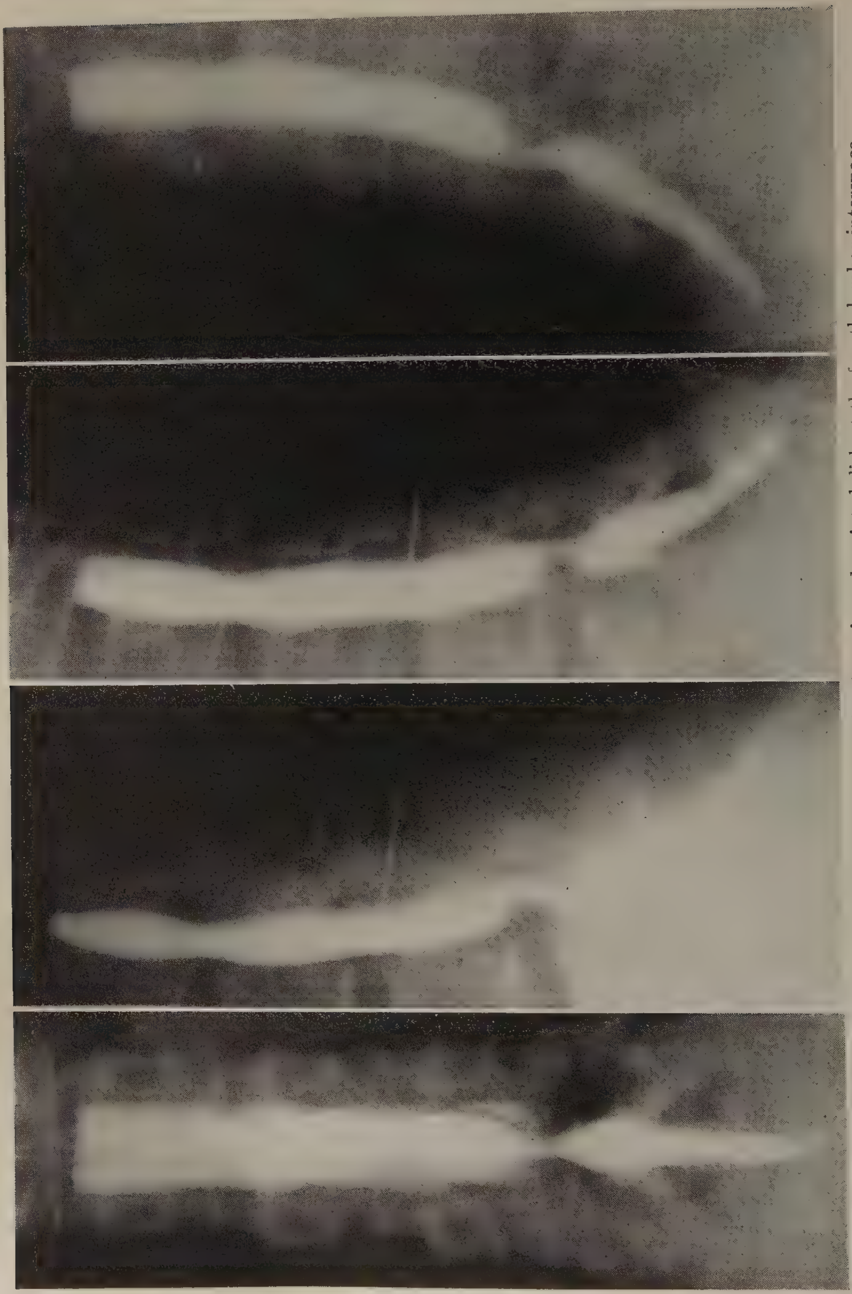

FIGURE 6. Routine upright roentgenograms showing a large herniated disk at the fourth lumbar interspace.

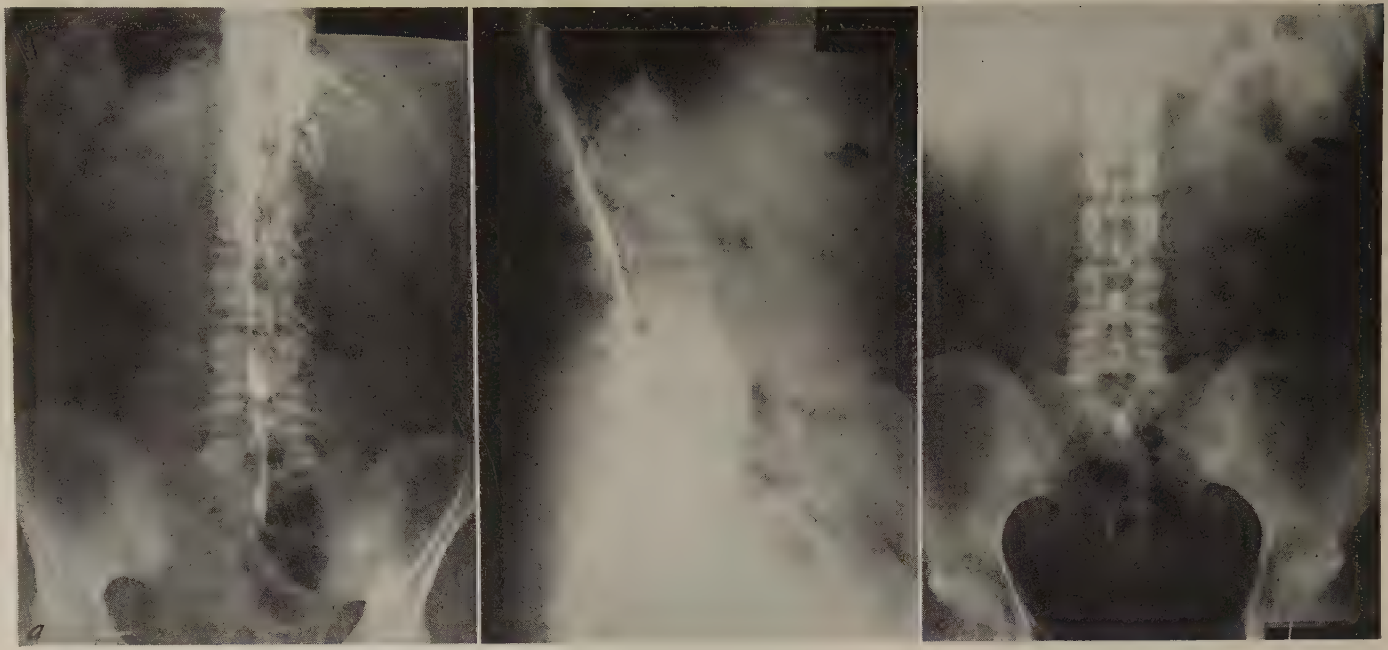

FIGURE 7. (*a*, *b*) Dye along the dura and nerve sheaths. (*c*) Same patient, eighteen months later; no dye was removed by aspiration.

ments secondary to degeneration of the disk itself. These do not represent herniation and, in our experience, are rarely productive of significant symptoms.

Hypertrophic bone spurs at the margins of the vertebral bodies occasionally are found to produce deformities in the oil column and clinically significant symptoms (FIGURE 5).

Herniated intervertebral discs were found at a single level in 124 cases (FIG-

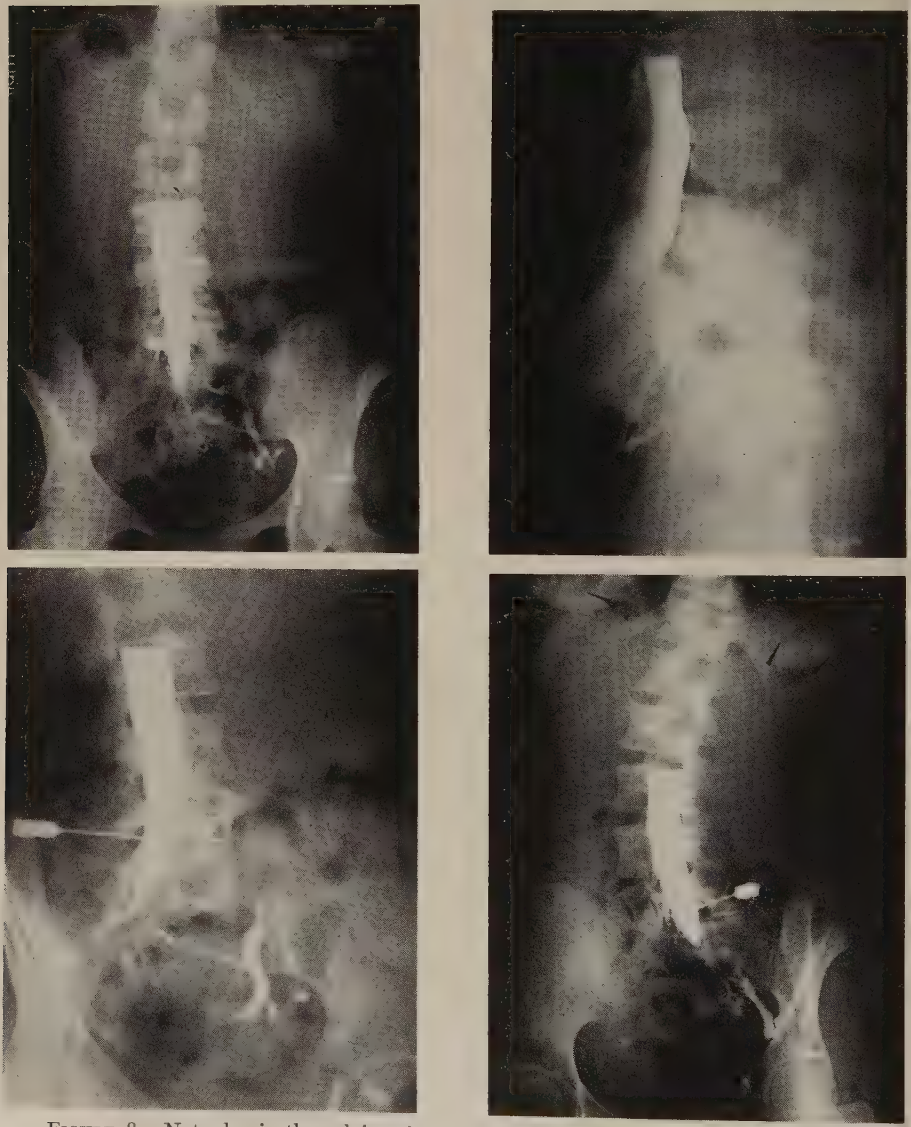

FIGURE 8. Note dye in the pelvic veins. Arrows indicate dye in arterioles in lungs.

URE 6) and at 2 levels in 11 patients in this group. In our experience there is a small number of patients who have had 3 interspaces with protruded disks.

The 14 instances of technical deviations due to errors in needle placement, while professionally embarrassing, produced no untoward clinical effects, immediately or later. In 1 case, 16 cc. of dye were injected intradurally, with dye traveling along the dura and the nerve sheaths (FIGURE 7*a*, *b*); no attempt was made to remove this. A follow-up film made 18 months later (FIGURE 8*c*) shows the residual dye. Absorption from the spinal canal itself was practically nil, and absorption from the intradural spaces was more rapid. This patient has had no clinical symptoms from this experience.

The spinal canal contains a rich venous plexus anteriorly and laterally. When the needle is advanced through the dura on the anterior side, the tip of the needle occasionally will enter 1 of these vessels. If dye is then injected it seems to be part intravenous and part intraspinal. Needle defects produced in the anterior wall of the dura and in a contiguous blood vessel in 2 patients produced a channel through which dye flowed from the canal into veins (FIGURE 8). This accident was not visible fluoroscopically or with the image amplifier, but was noted on the films taken in the upright position. In neither case was any clinical effect produced. In 1 case the dye is visible in the small pulmonary arterioles in the base of the lungs. Subsequent chest films showed no evidence of radiopaque agent, and no pulmonary symptoms were encountered.

Summary

Large-volume myelography has not proved harmful in any way despite an occasional misadventure. The diagnostic accuracy of the method is both radiologically and surgically very satisfactory. Pantopaque has proved to be an innocuous dye from the symptomatic point of view, even when technical deviations occur. We have observed no adverse clinical effects that could be attributed to the radiopaque agent itself. The one drawback to this medium is its lack of rapid absorption from tissues and spinal fluid.

The medicolegal implications of residual dye are frightening. From the medical viewpoint, residuals of this dye preclude the use of radioactive-iodine tracer studies for the lifetime of the patient.

A new radiopaque agent for myelography is urgently needed. It should have all of the excellent qualities of Pantopaque and, in addition, must be absorbed from spinal fluid and from body tissues at a rapid rate.

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ORAL 76 PER CENT SODIUM AND METHYLGLUCAMINE DIATRIZOATES, A NEW CONTRAST MEDIUM FOR THE GASTROINTESTINAL TRACT*

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Although barium sulfate remains the standard contrast medium for roentgenographic examination of the gastrointestinal tract, there has been a continuing search for a superior opaque medium, particularly for emergency situations. In 1955, Canada[1] reported the use of Urokon in the alimentary canal. In 1956 Davis *et al.*[2] described the use of Urokon (35 to 70 per cent) for examination of the gastrointestinal tract. Lowman and Epstein have used Hypaque with good results.[3-5] Epstein[4] has also reported on the use of Renografin in the digestive tract.

Recently oral 76 per cent sodium and methylglucamine diatrizoates became available for use as an opacifying medium in the gastrointestinal tract. Continuing experiences with this medium for approximately one and one-half years have given us some basis for evaluating and comparing this substance with barium sulfate. This report presents the advantages, disadvantages, indications, and contraindications in the use of this contrast agent.

Properties

Oral sodium and methylglucamine diatrizoates is a lemon-flavored, aqueous solution of the solubilized salt of 3,5-diacetylamino-2,4,6-triiodobenzoic acid and contains 59.7 per cent renographic acid and 37.0 per cent iodine. This substance has a viscosity of 10.4 cp. 25°C., and a pH of 6.0 to 6.5. No toxic effects were encountered in its thorough testing on dogs.

The Ideal Contrast Medium

The ideal contrast medium for use in roentgenographic examination of the gastrointestinal tract should be: nontoxic in the digestive tract or when accidentally introduced outside of the alimentary canal; nonabsorbable from the gastrointestinal tract; physiologically inert in the gastrointestinal tract; water-soluble; readily and completely eliminated from the digestive tract; absorbable when unintentionally inserted into the pleural or peritoneal cavities; and stable on prolonged storage. It should maintain complete solubility, be homogeneously radiopaque, have an optimum degree of radiopacity and low viscosity, be miscible with body fluids, palatable when orally administered, have ease of preparation, and be inexpensive.

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* The investigation reported in this article was aided by a grant from E. R. Squibb & Sons, New Brunswick, N. J.

Disadvantages, Limitations, and Complications Following the Use of Barium Sulfate

Barium sulfate is not a true water-soluble medium since the particles do not remain discrete and tend to precipitate. Inasmuch as it is not soluble, water is absorbed (particularly in the colon), with the danger of inspissation and impaction.

Barium sulfate may be relatively unsuitable for outlining minute fistulous tracts. In the presence of intestinal-tract perforation, the oral or rectal route of administration may introduce barium sulfate into the peritoneal cavity. Although deleterious effects from barium in the peritoneum are open to question, it is preferable to have an absorbable medium in the peritoneal cavity.

There is danger of aspiration of barium into the lungs in such conditions as tracheoesophageal fistula, achalasia, neoplasm of the esophagus or lung, esophageal stricture, and pyloric stenosis in infants. Here again, there is debate

TABLE 1

TYPES OF CASES IN WHICH ORAL 76 PER CENT SODIUM AND METHYLGLUCAMINE DIATRIZOATES HAVE BEEN USED

Large-bowel obstruction	27
Upper gastrointestinal obstruction	24
Gastrointestinal bleeding	15
Postoperative cases; resection or perforation of gastrointestinal tract	12
Foreign body	8
Megacolon	3
Total	89

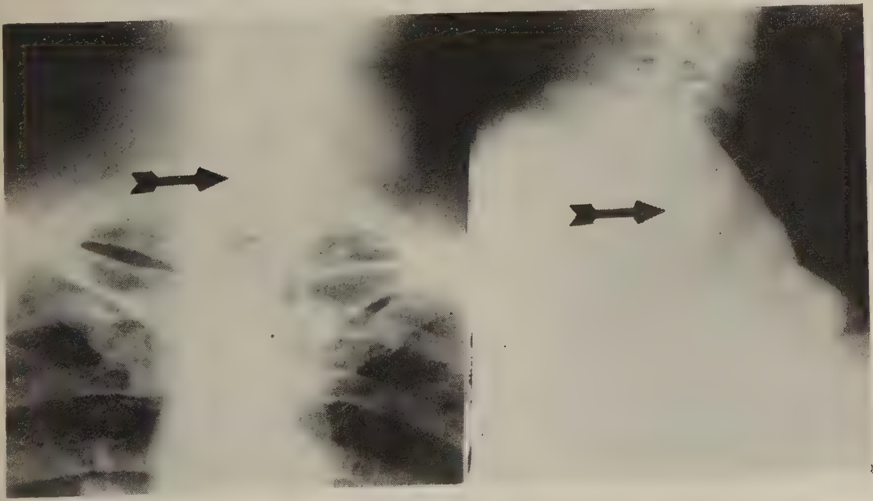

FIGURE 1. Arrest of Renografin-opacified cotton ball (arrows) by nonopaque foreign body in the cervical esophagus.

about the danger of aspirating barium into the lungs; again, however, the presence of a water-soluble medium in the lungs is preferable.

The occurrence of barium granuloma in the rectum and appendix is a rare complication.

Barium sulfate in the gastrointestinal tract may serve as an annoying contrast medium in the event of future examinations; for example, by obscuration of the urinary tract and spine.

Clinical Material

We have carried out studies of the gastrointestinal tract in 89 patients, using oral diatrizoates sodium and methylglucamine 76 per cent. TABLE 1 refers to

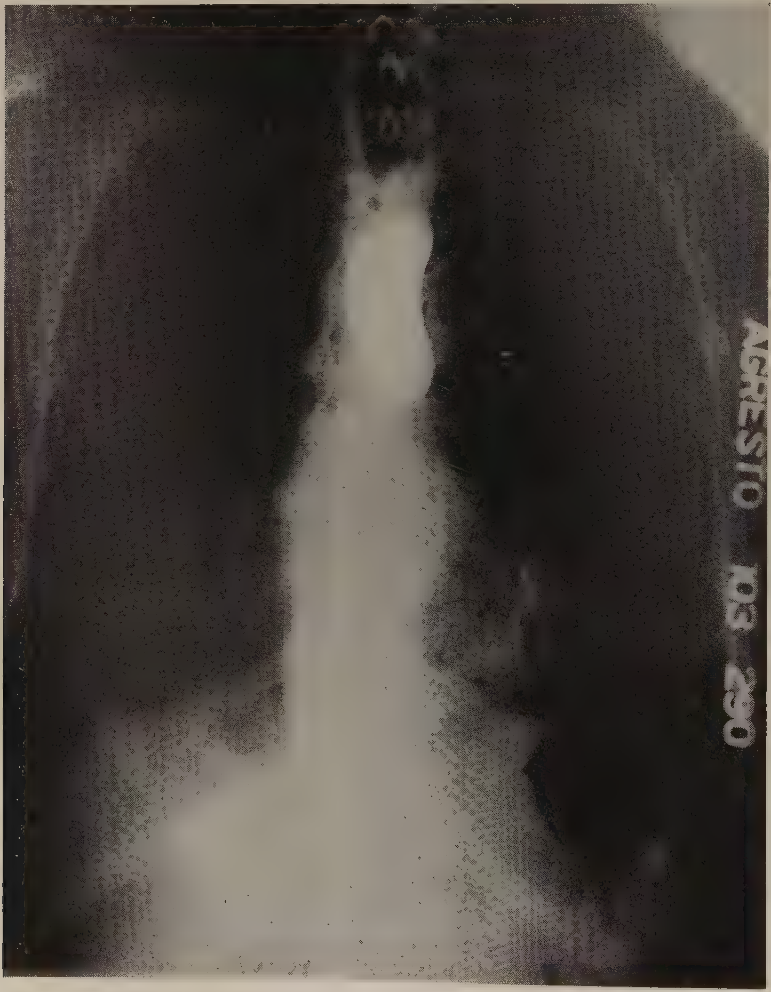

FIGURE 2. Carcinoma of mid-third of esophagus in a patient with symptoms of complete obstruction.

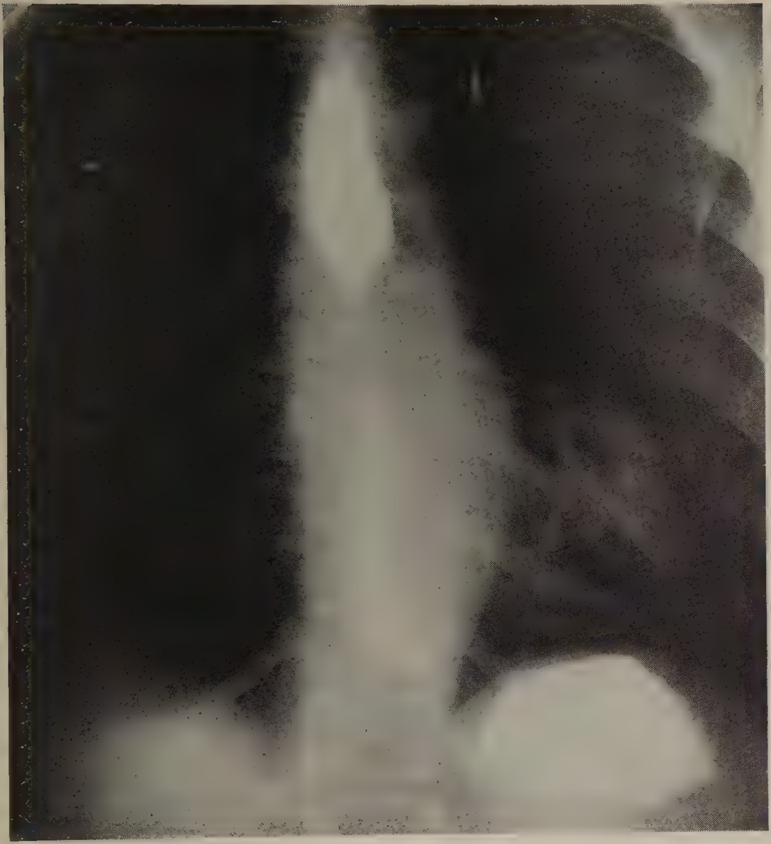

FIGURE 3. Carcinoma of mid-third of esophagus.

the numbers and general types of cases in which this medium was used. In most instances, this substance* was utilized in an undiluted form, although in some cases a 50 per cent dilution produced adequate radiopacity. This dilution was found to be both practical and adequate in emergency examinations of the colon for obstruction, where a large volume of contrast medium is frequently necessary.

Techniques

A volume of oral 76 per cent Renografin equal to the usual volume of barium sulfate in water for upper gastrointestinal-tract examination and barium enema studies was used. As indicated, in most instances the medium was given undiluted. The usual fluoroscopic and roentgenographic examinations were carried out in all instances. FIGURES 1 through 19 are illustrative of this case material.

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* In the interest of brevity, during the remainder of this report this substance will be called oral 76 per cent Renografin.

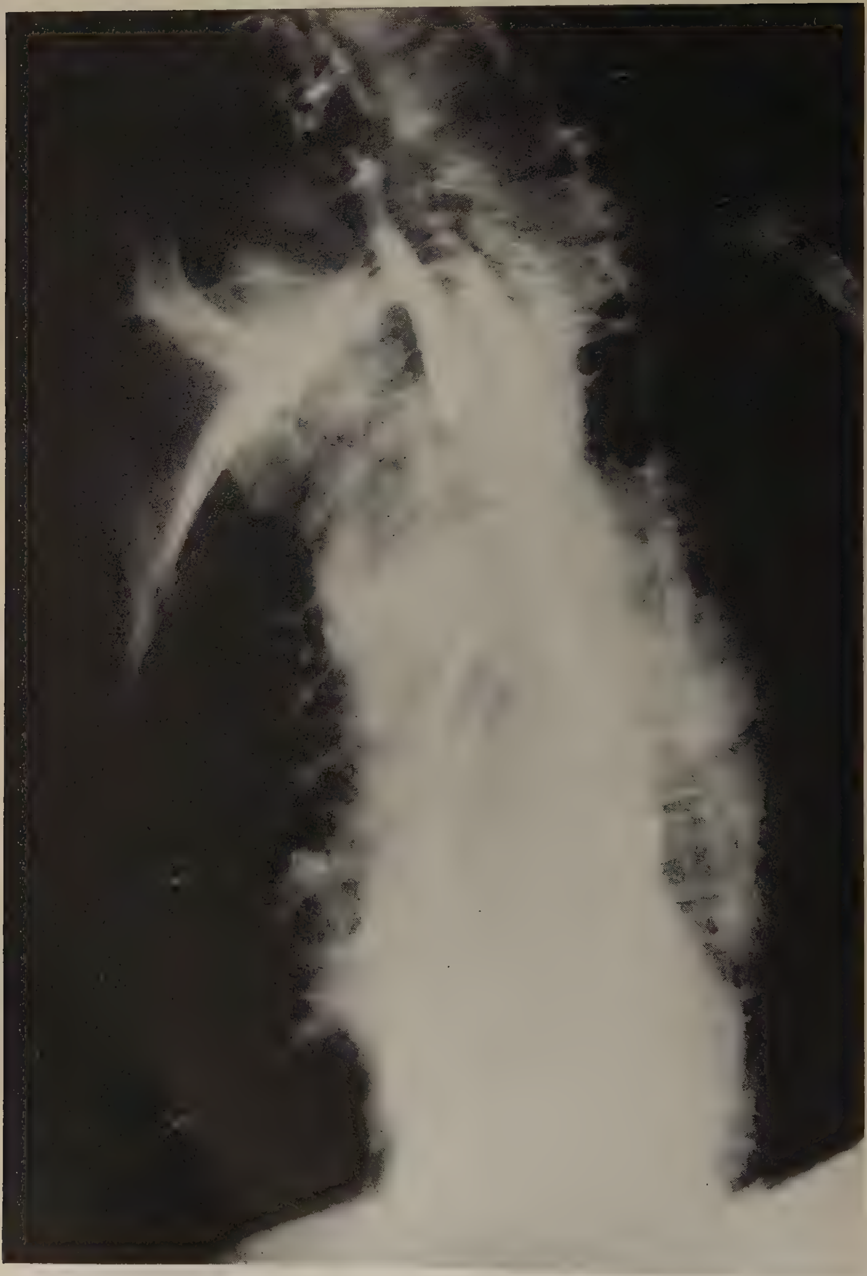

FIGURE 4. Renografin swallow in case of laryngeal carcinoma. The opaque medium has been aspirated and outlines the trachea and bronchi.

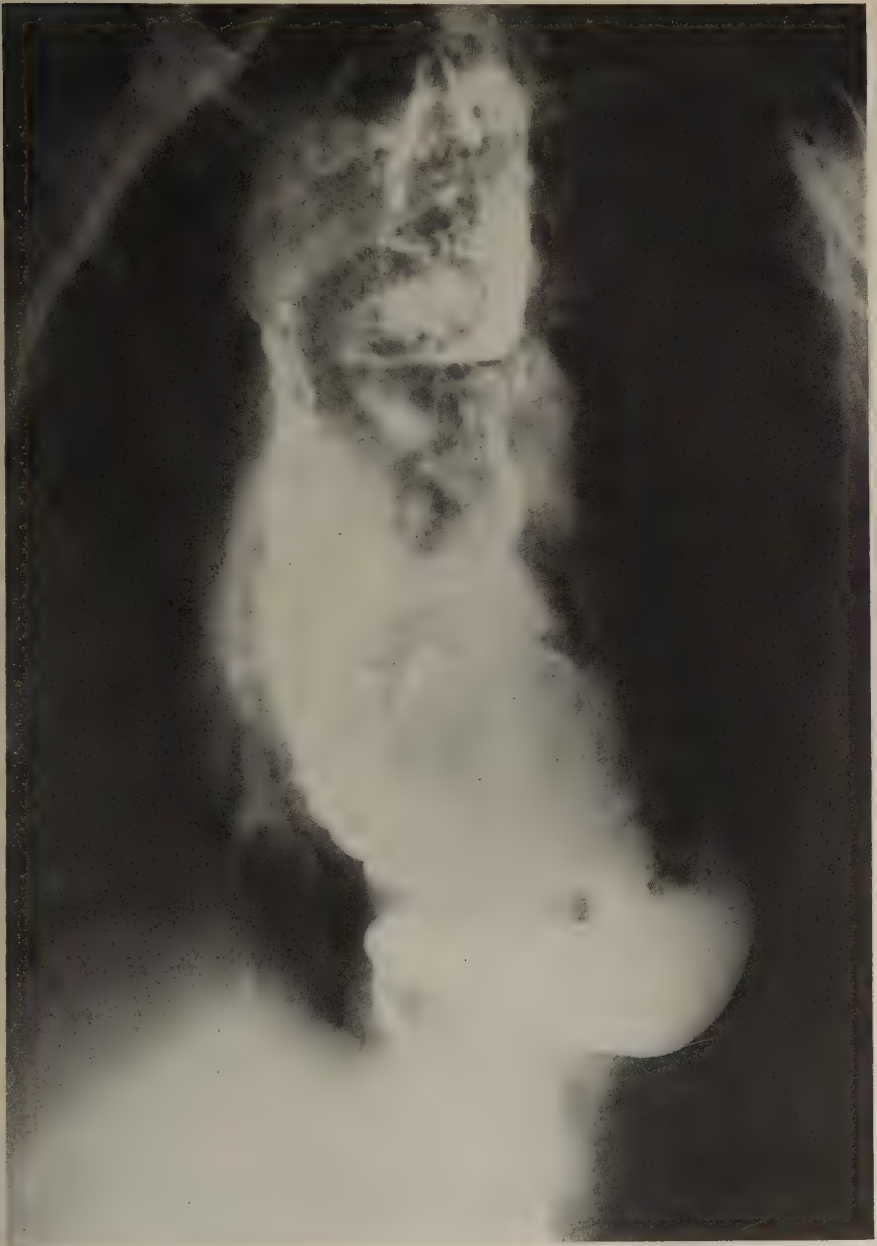

FIGURE 5. Achalasia of the esophagus demonstrated with Renografin.

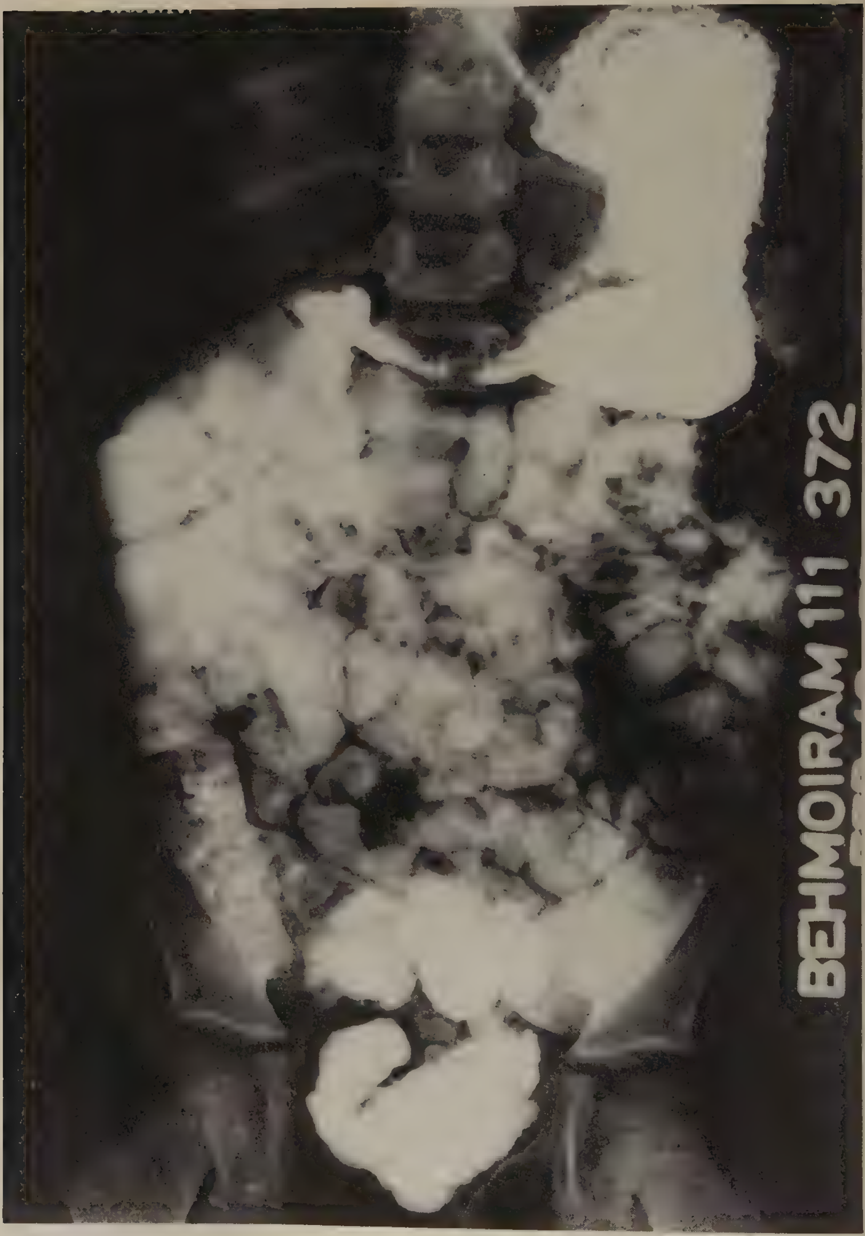

Figure 6. Normal upper gastrointestinal tract study. Accelerated motility is demonstrated by opacification of the stomach and small and large bowel. The dilution effect is demonstrated in the small intestine with a resulting poor mucosal pattern.

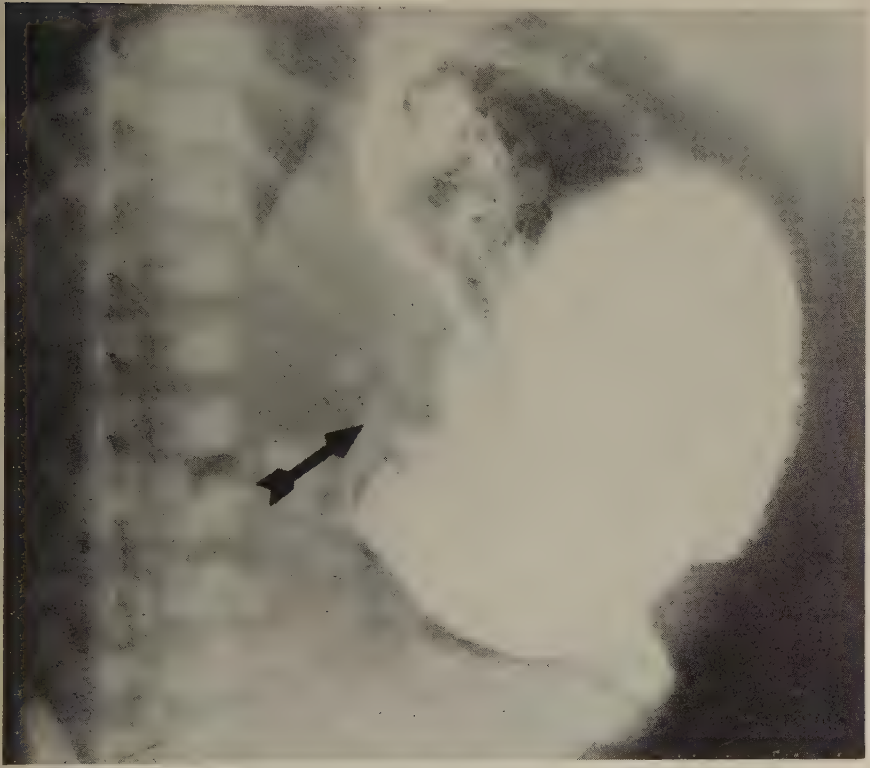

FIGURE 7. Pyloric stenosis in an infant. The elongated and narrowed pyloric canal is outlined with oral 76 per cent Renografin.

Although water-soluble contrast media (that is, sodium acetrizoate and diatrizoate sodium) have been used in examination of the digestive tract, oral 76 per cent Renografin is the first medium to be prepared specifically in liquid form for such use. Because of its palatability, direct ingestion is feasible, whereas other such media have required intubation for introduction into the upper gastrointestinal tract.

The medium is water-soluble, palatable, and of low viscosity and satisfactory radiopacity, with no toxic effects. In 3 cases we noted a significant excretion of the opaque medium through the urinary tract, which permitted adequate visualization of the collecting system of the kidneys and the urinary bladder (FIGURE 20). Oral 76 per cent Renografin is uniform in its radiopacity and does not settle on standing. It is easily miscible with blood, so that it can be used in cases with bleeding. Gastric emptying and bowel motility are accelerated, so that the entire small bowel may be visible in a short time. This medium is readily available and requires no preparation.

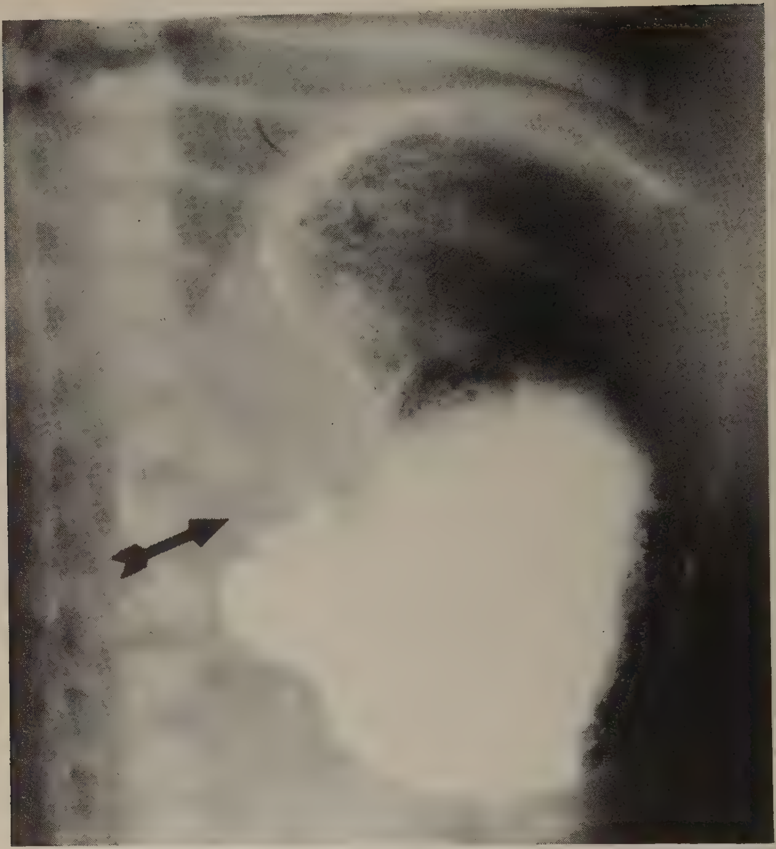

FIGURE 8. Pyloric stenosis in an infant.

Indications

The indications for the use of oral 76 per cent Renografin in the gastrointestinal tract are: (1) emergency examination, particularly of the esophagus, stomach, and colon to localize or to confirm the site of obstruction; (2) impending perforations, that is, peptic ulcer or diverticulitis; (3) foreign bodies, particularly in the pharynx and esophagus (when oral 76 per cent Renografin is used, the endoscopist finds no obscuration of the foreign body or the pharyngoesophageal walls, as with barium); (4) roentgenographic studies, immediately postoperative, following resection, anastomosis or both; (5) acute and massive bleeding (barium may be used, but a water-soluble medium offers distinct advantages under certain circumstances, such as those involving a danger of aspiration in debilitated patients and where there is impending perforation); (6) megacolon, where stasis of barium may result in serious inspissation with obstruction, while oral 76 per cent Renografin is easily evacuated; (7) disordered swallowing mech-

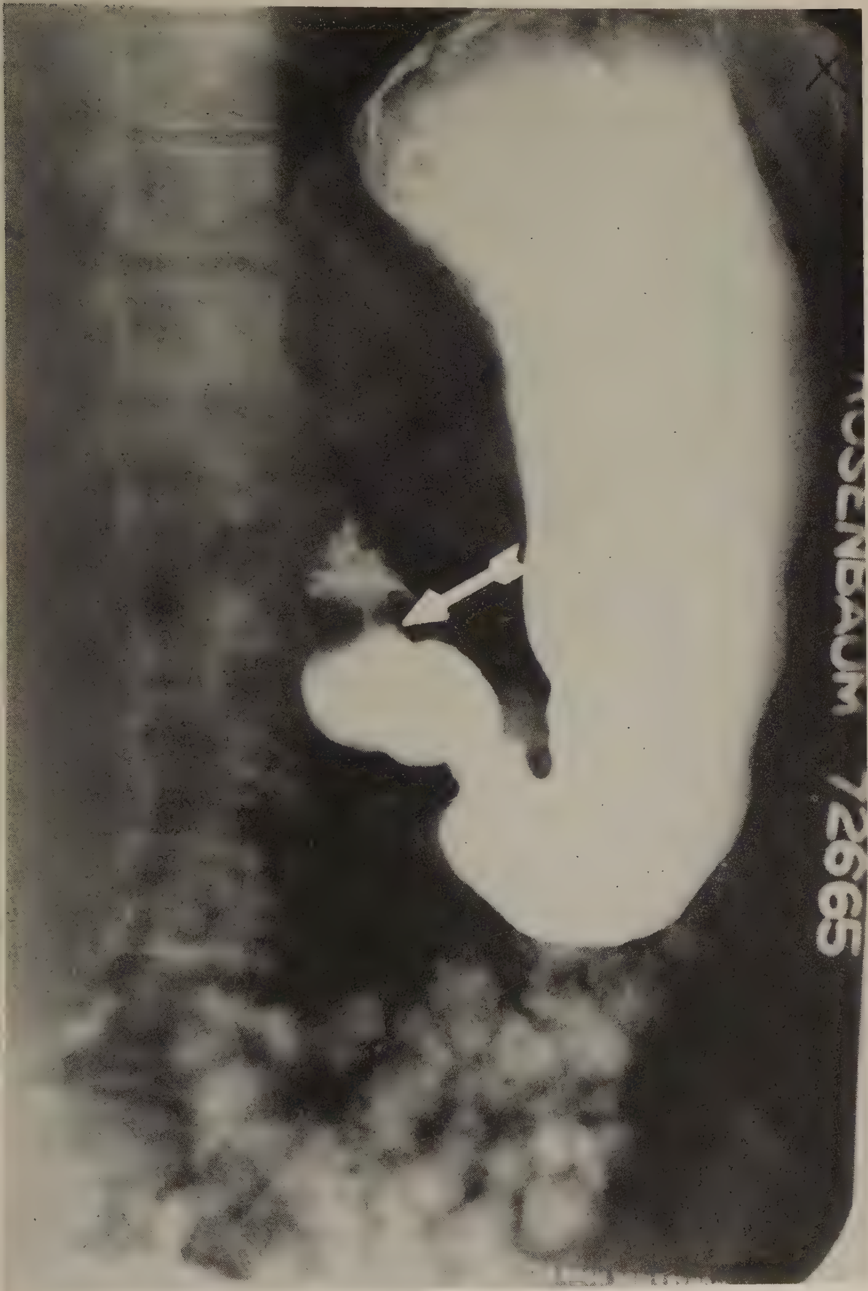

Figure 9. Pyloric canal peptic ulcer. Note dilution effect in the small intestine.

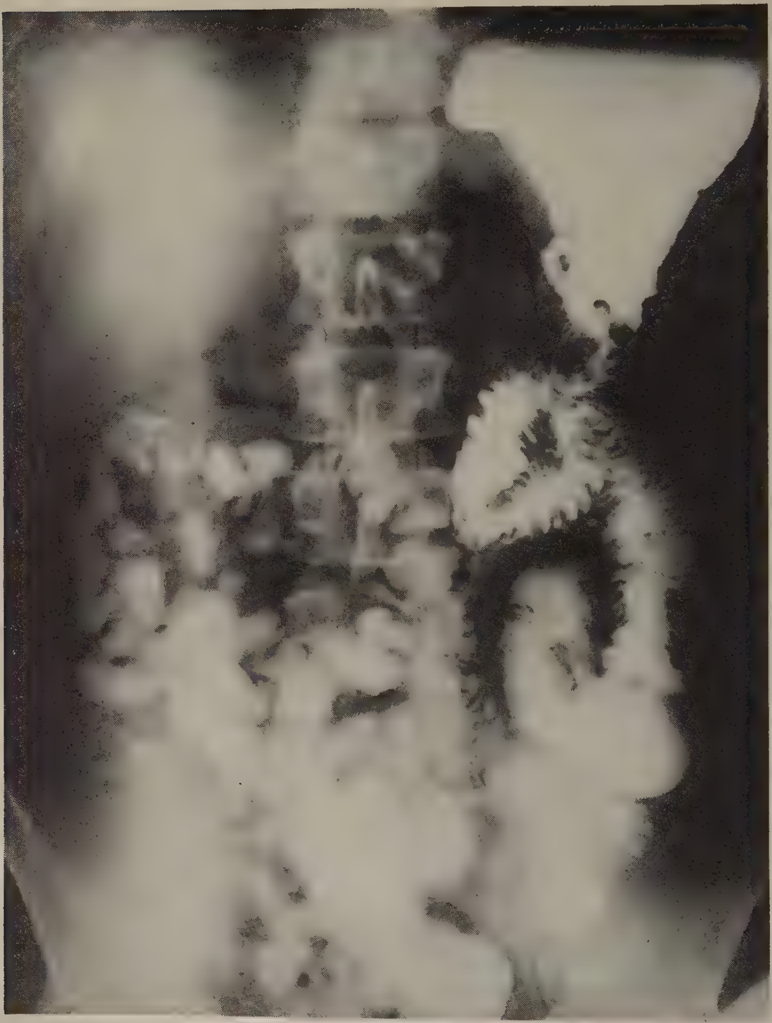

Figure 10. Postoperative study of patient with subtotal gastrectomy with gastroenterostomy.

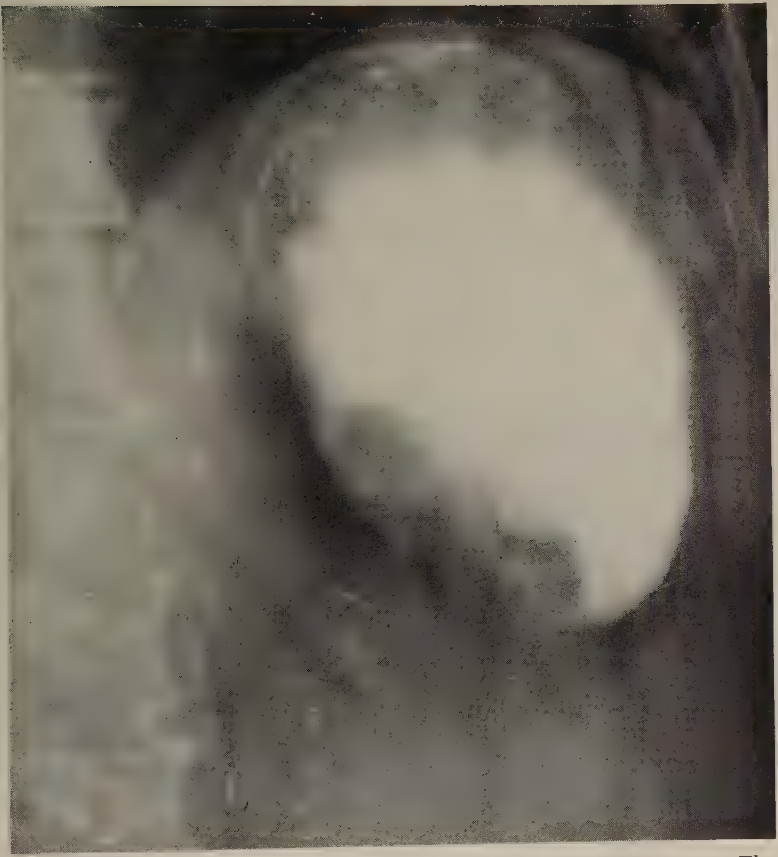

FIGURE 11. Recurrent carcinoma of the stomach after subtotal gastrectomy. The polypoid tumor mass obstructs the gastroenterostomy.

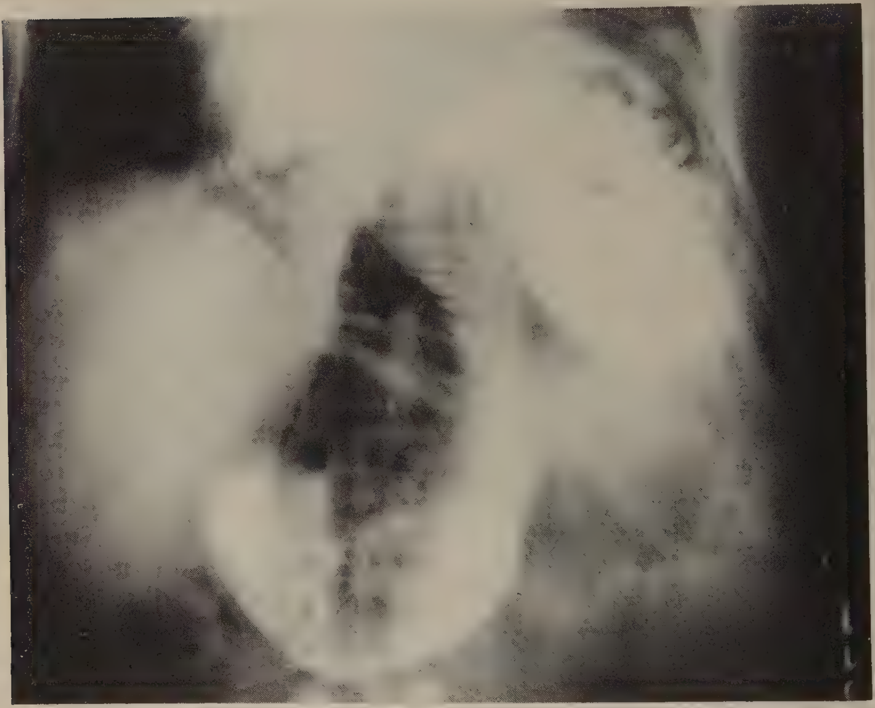

Figure 12. Postoperative examination following esophagojejunostomy with obstruction of the efferent loop and marked dilatation of the afferent loop.

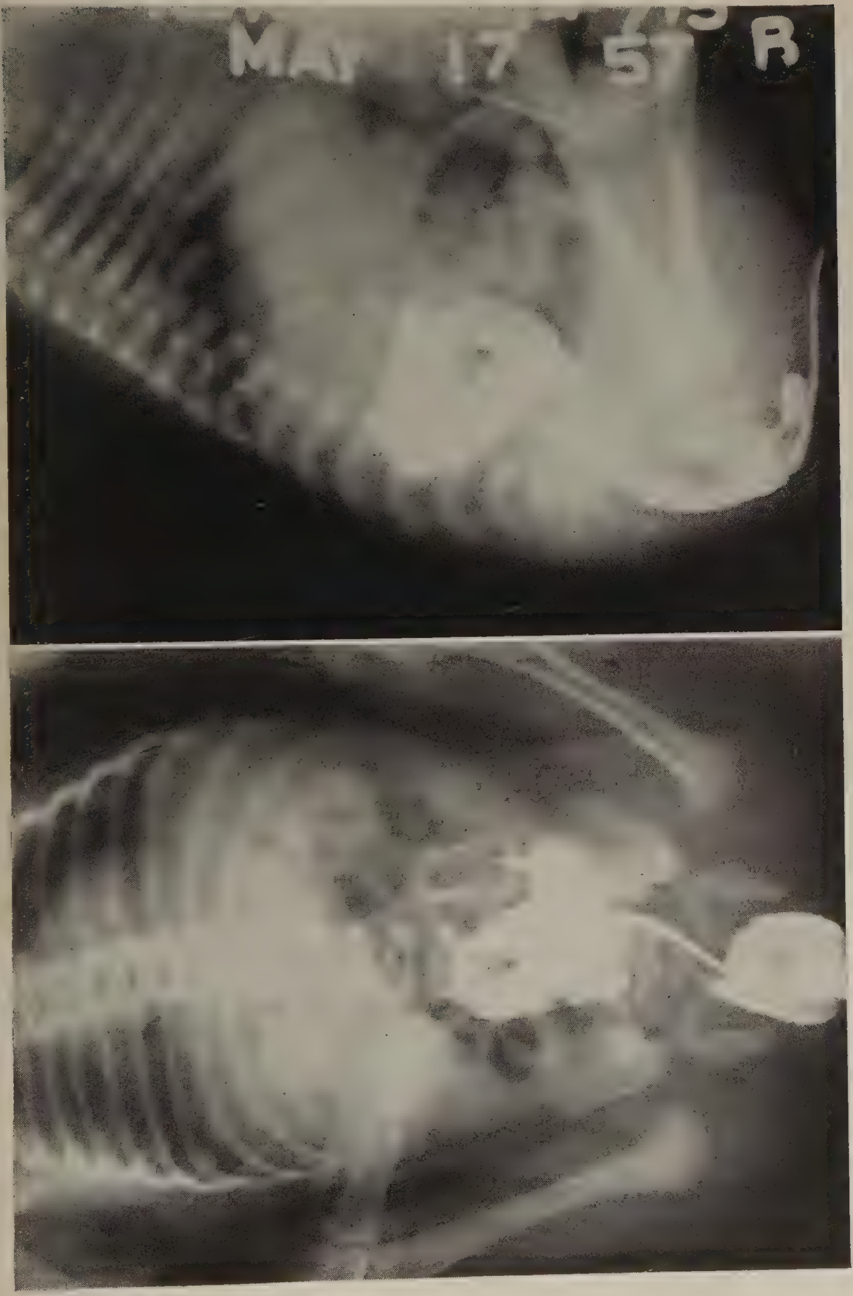

FIGURE 13. Renografin enema demonstrating a rectovaginal fistula (left) in frontal and (right) in lateral projections.

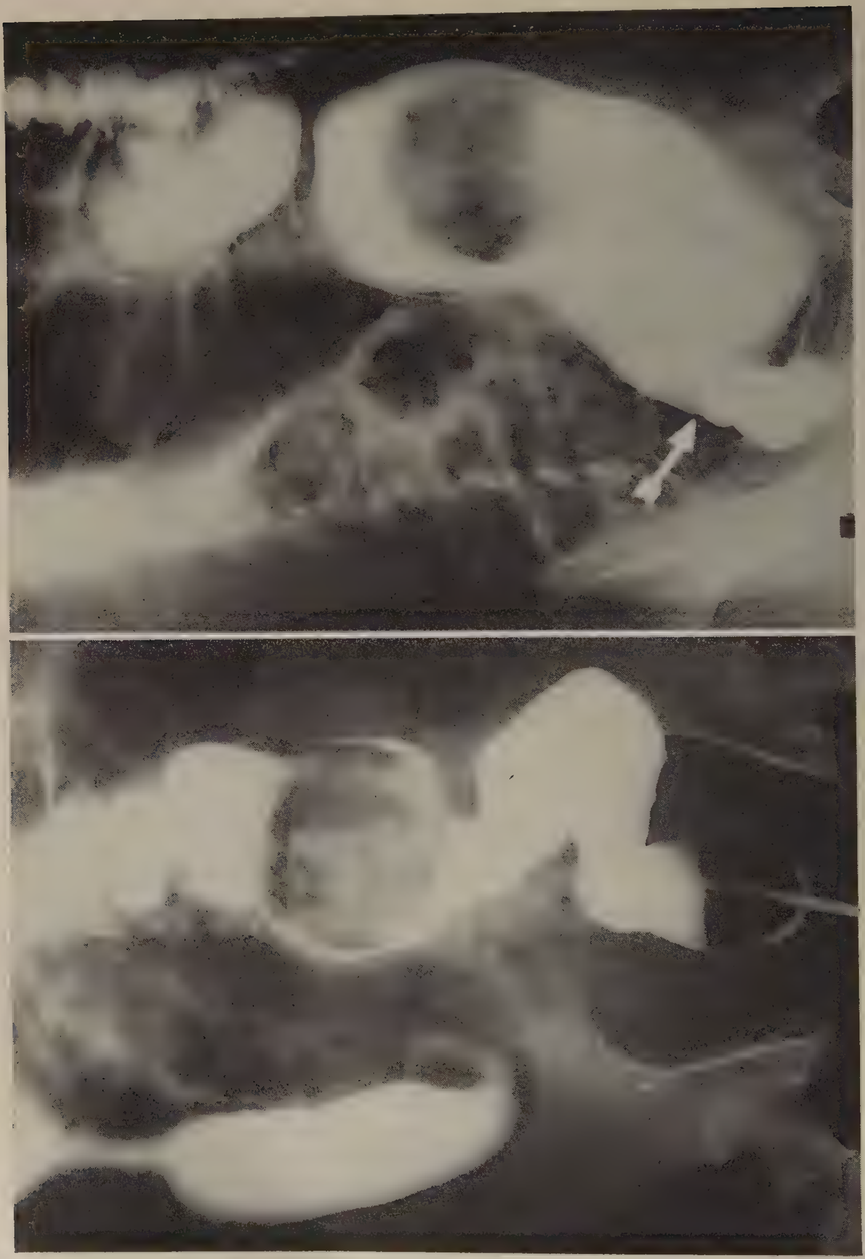

FIGURE 14. Renografin enema in megacolon. Left: frontal projection showing a dilated descending colon with a large scybalum in the sigmoid colon. Right: oblique view showing site(arrow) of narrowed aganglionic segment.

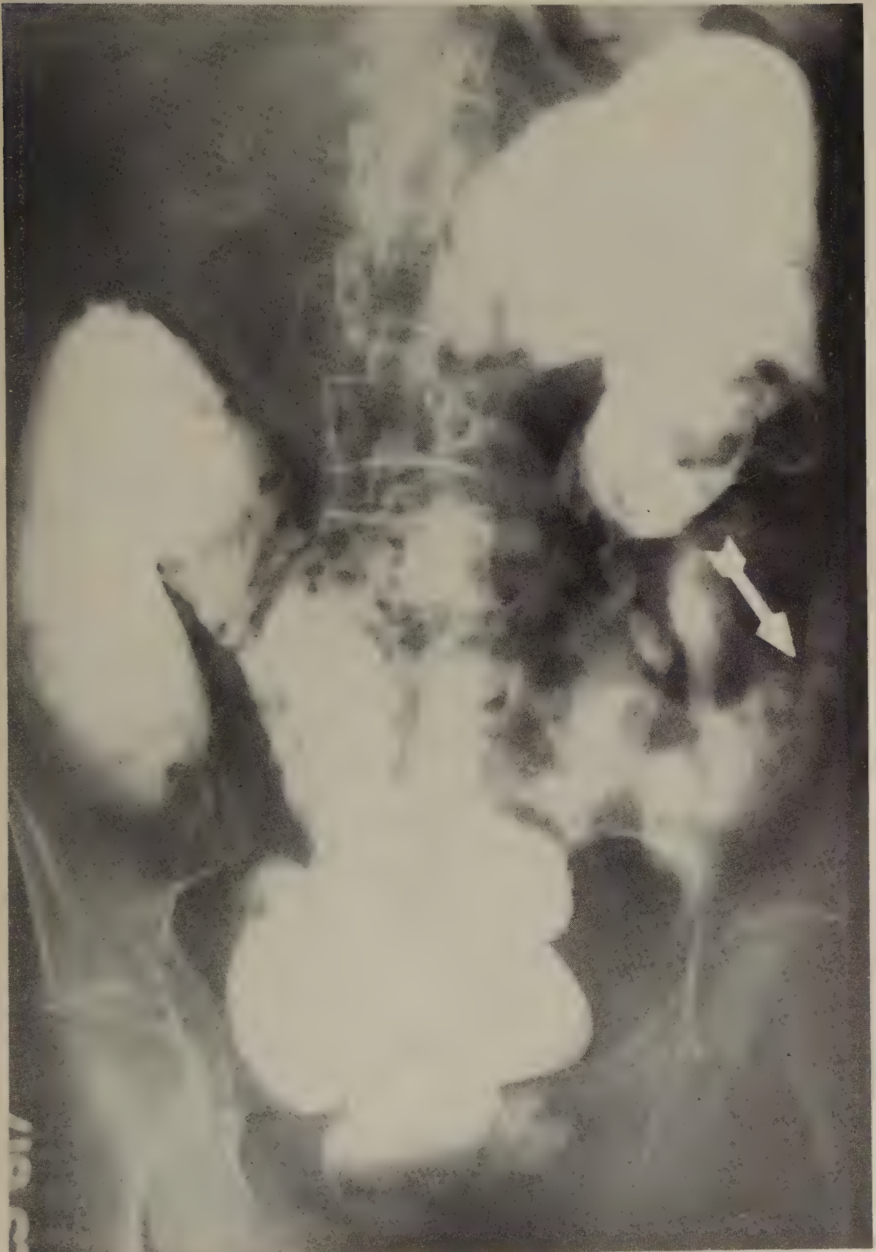

FIGURE 15. Ulcerative colitis with multiple polyps and pseudopolyps, best seen in the proximal transverse colon. Note site of fistulous tract (arrow). The right upper urinary tract is opacified as a result of intestinal absorption of the renografin.

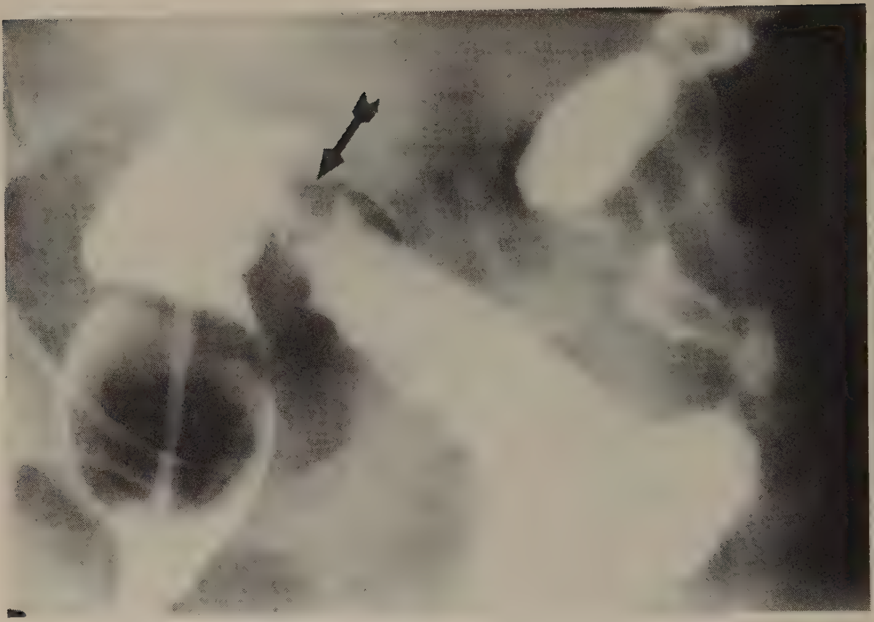

Figure 16. Carcinoma of sigmoid colon.

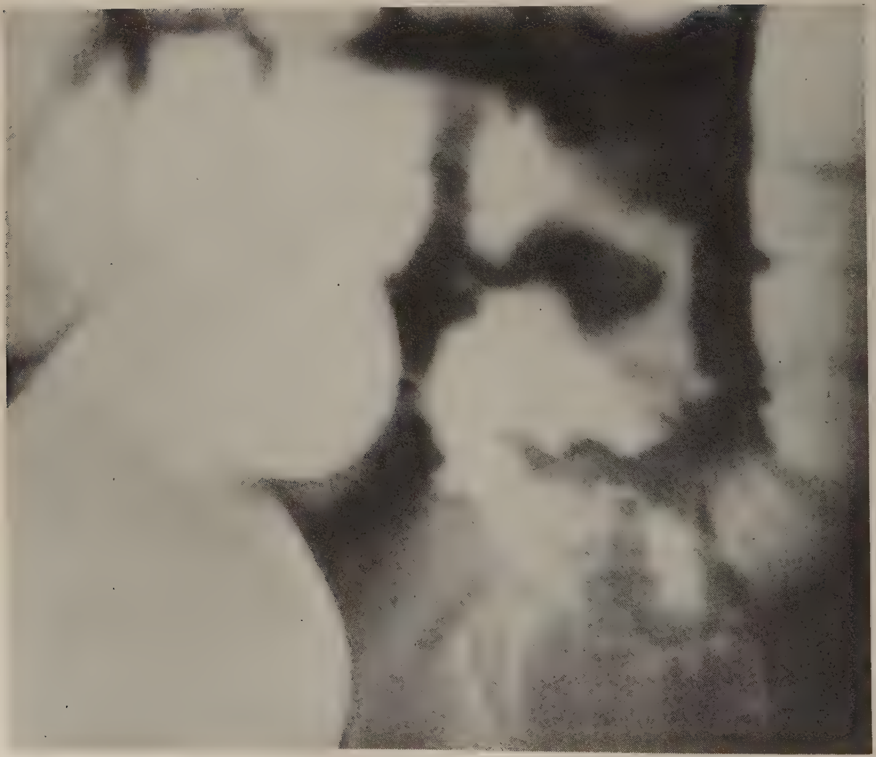

Figure 17. Carcinoma of the sigmoid colon with diverticulosis proximal to the neoplasm.

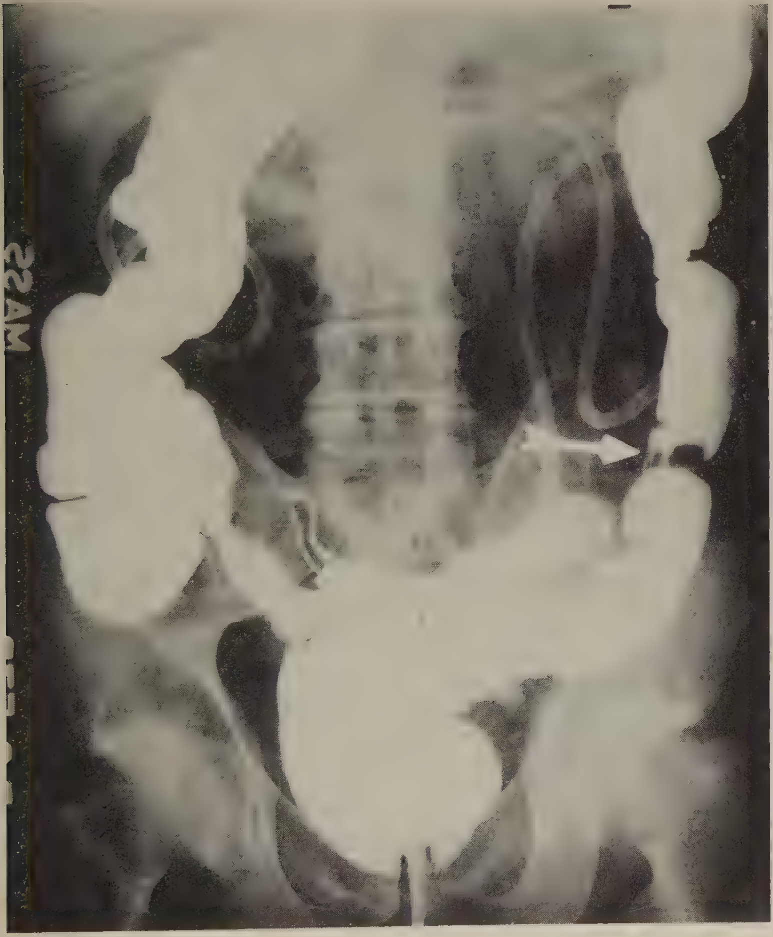

FIGURE 18. Carcinoma of descending colon.

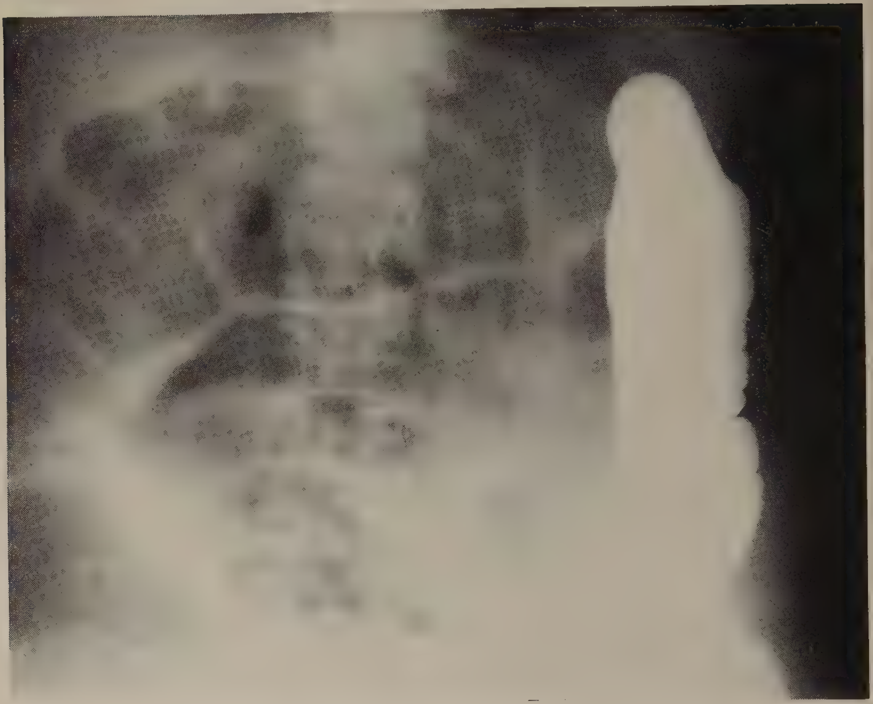

FIGURE 19. Emergency Renografin enema; carcinoma of the splenic flexure with complete obstruction.

anisms, as in neuromuscular disturbances and central nervous system abnormalities; (8) visualization of sinus tracts and fistulae where barium is potentially dangerous; and (9) outlining of abscess cavities.

Contraindications and Disadvantages

Although there has been some apprehension that this medium might aggravate existing diarrhea or active colitis, we have not found this to be true and are not aware of significant contraindications to its use. In view of the excessive absorption seen in three cases, one might question the use of this medium in instances of severe hepatic or renal insufficiency. However, our experiences with Renografin as a urographic medium[6, 7] are such that we seriously question the likelihood of any untoward complications.

The dilution of oral 76 per cent Renografin in the small bowel does not permit a satisfactory visualization of the mucosa. There is an outpouring of fluid activated by its use so that poor mucosal detail is found in the small intestine. Similarly, oral 76 per cent Renografin increases peristaltic activity and the irritability of the bowel. It is probable that only gross lesions in the small in-

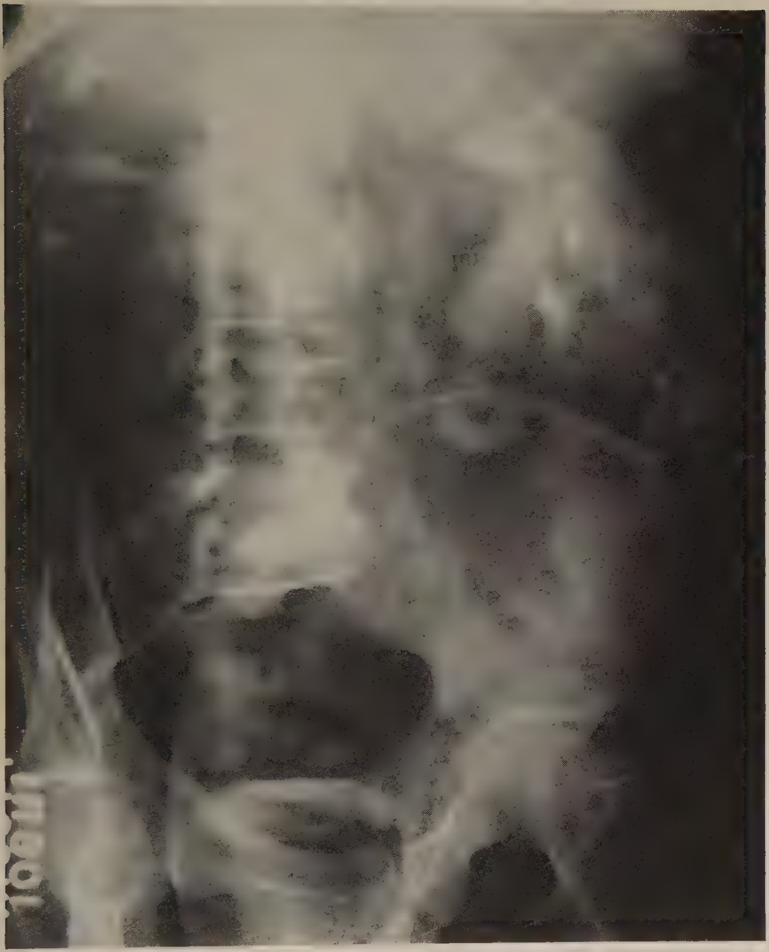

FIGURE 20. Visualization of the collecting systems of both kidneys via intestinal absorption of Renografin. A marked left pyelocaliectasis is probably secondary to pelvic inflammatory disease. This roentgenogram was obtained after evacuation of a Renografin enema.

testine can be diagnosed. The large bowel evacuates this medium completely, interfering with adequate mucosal visualization. Air-contrast studies are also relatively unsatisfactory.

This medium is of relatively low viscosity, so that it may easily pass through zones of incomplete obstruction, for example, pyloric stenosis in infants, and achalasia. The cost of this medium is considerably greater than that of barium sulfate. However, in considering the advantages in selected situations, cost should be of secondary importance. As further experience is gained, the cost may be reduced.

Summary and Conclusion

Oral 76 per cent sodium and methylglucamine diatrizoates has proved to be a satisfactory opaque medium for roentgenographic examination, particularly of the gastrointestinal tract in selected instances. The safety of this medium has been established and the advantages and disadvantages, indications, and contraindications are discussed.

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DIATRIZOATE SODIUM

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We first used Hypaque (diatrizoate sodium) while examining fifty patients in a routine test for another medium for intravenous urography. The superiority of this agent to all those previously used quickly became obvious. The urographic shadows were of superb density and clarity, and there was a striking absence of unpleasant reactions. Among a number of our patients who had had one or more urograms with other media there were several very sensitive and high-strung individuals who approached the repetitition of the procedure with some alarm. After receiving the Hypaque all remarked about the absence of unpleasant reaction.

Because of its obvious superiority, we soon began to use this medium to the exclusion of all others. At the Veterans Administration Hospital, Hines, Ill., we have used Hypaque in 7144 cases to September 1, 1958.

Previous Experience with Other Urographic Media

Diodrast (iodopyracet) had been used in a series of 16,000 cases from 1947 to 1956 at the Veterans Administration Hospital. There were no fatalities, but serious reactions were occasionally encountered. The injection was usually accompanied, if not by a reaction, by an unpleasant sensation of warmth and a feeling of apprehension; nausea and vomiting were common. The films were reasonably good.

In private practice we had used Neo-Iopax (sodium iodomethamate) exclusively for seven years because, after several unpleasant experiences with Diodrast, we feared possible severe or fatal reactions. The systemic reactions with Neo-Iopax were less severe, and the opacification and clarity of the shadows seemed to be better than with Diodrast. Most patients, however, experienced severe arm and shoulder pain at the site of injection because of vein cramp. This often occurred in spite of measures recommended to prevent it. Many patients had subsequent phlebitis at the site of injection, evidenced by a palpable, tender thickening of the vein and discomfort, which persisted for many weeks or months. This was such an unpleasant experience for some that they remembered it and remarked about it years afterward. To them the intravenous urogram had been an ordeal more severe than the subsequent cystoscopy.

We had used Urokon (sodium acetrizoate) in only a small series of cases (approximately 150) in spite of the many recommendations at the time as to its excellence. This was due largely to inertia on our part. We employed the 70 per cent solution in approximately 75 cases and in 35 aortograms. Although we used no preventive measures (such as Chlor-Trimeton or Benadryl) to combat reactions, we had no serious or alarming experiences with it. However, in the hands of many others this medium has produced so many serious or actually fatal reactions (reports of which have been made by word of mouth, but not published) that it is our feeling that this agent, although giving excellent urograms, is very toxic; as a result, we have been reluctant to use it further. Its reported successful use without serious reactions in large series of cases where antihistaminic agents are employed does not minimize its potential dangers. Pendergrass *et al.* (1957) call attention to the fact that of the 61 immediate deaths (since 1952) due to the use of intravenous urographic media, Urokon had been used in 36 cases.

Reactions with Hypaque

In our first 1000 cases in which Hypaque was employed we encountered 29 reactions; these were all mild and distributed as follows: vomiting, 12; nausea, 13; urticaria, 4; and generalized tremors, 1.

With case number 1003 there was a very severe reaction, which almost resulted in a fatality. Fifteen minutes after the injection a circulatory collapse ensued. Supportive measures, including oxygen, Levophed, intravenous therapy, and the combined vigorous attention of several members of the house staff for 4 hours were necessary to save the patient's life.

We had become complacent about the innocuous nature of Hypaque until this occurred. An intravenous injection of any sort always carries a potential hazard with it, and this is especially true if the injected substance is an iodine compound. Subsequently we had, in a private patient, a moderately serious reaction accompanied by laryngeal and orbital edema.

In April 1958, after using the medium in more than 6500 cases, we had a fatal reaction. A 29-year-old white male had had calculi removed from his right kidney 7 years previously. Subsequently, intravenous urograms were made on 4 separate occasions without incident. Two days prior to his admission to the hospital, the patient experienced pain in the right flank. Leukocytes and erythrocytes in moderate number were present in the urine. A scout film showed calcific shadows in the region of the left kidney. Intravenous urography was scheduled for April 28, 1958. With the patient supine on the table, 25 mg. of Benadryl was given intravenously. After an interval of approximately 5 min., 30 cc. of 50 per cent Hypaque solution was given intravenously in approximately 1 min. No untoward reaction was noted immediately after the injection. About 2 to 3 min. after the injection it was noted that the patient was having a reaction; he became cyanotic, and his respirations were slow, deep, and labored. Foam appeared at his mouth and nose, obviously the result of a rapidly developing, acute pulmonary edema. An injection of 0.5 cc. of 1:1000 adrenaline was given intramuscularly and, within a matter of minutes, an additional 0.5 cc. was given intravenously. The mouth and nasopharynx were aspirated and, after the insertion of an airway, the administration of oxygen by mask was attempted. This was ineffective because of the massive quantity of foam exuding from the respiratory tract. An endotracheal tube was quickly passed, and an attempt was made again to administer oxygen through the tube. This was again ineffective because of the massive secretions. Atropine and Levophed were given intravenously. All efforts failed to produce a response and the patient promptly expired.

Members of the anesthesia department had been called upon the first evidence of a severe reaction. They responded within 5 min. and although they began treatment of the patient without delay, he expired within 30 min.

Autopsy revealed left renal calculi, severe pulmonary edema, and pronounced congestion of the heart, lungs, brain, kidneys, liver, spleen, and gastrointestinal tract.

After this fatality we immediately conferred with E. J. Foley of the Winthrop Laboratories, New York, N. Y., who called our attention to the statistical study on reactions presented by Pendergrass *et al.* at the Annual Meeting of the Radiological Society of America in November 1957. According to these authors, 1,500,000 urographic doses of 50 per cent Hypaque were administered in the United States from January 1955 through June 1957, with 7 fatal reactions. This represents an incidence of 1 in 214,285.

Some of these deaths were ascribed by the attending physicians to the patients' disease, to uncertain cause, or both. This would tend further to reduce the ratio of the fatalities.

Whatever the cause and however low the general incidence, the occurrence of a fatality during a presumably innocuous diagnostic procedure is always a harrowing experience and very difficult to explain to the family of the unfortunate patient.

Comparison with Other Urographic Agents

In spite of the apparently innocuous nature of Hypaque for the great majority of patients, the occurrence of a near-fatal reaction after the first 1000 cases and a subsequent fatality after 6500 cases gave cause for sober reflection. Considering the actual numerical incidence, as previously discussed, this medium is probably far safer than others, with the possible exception of Renografin. We were not sure how it compared with the other media with regard to density of shadows and quality of urograms and, therefore, we determined to run a series of 50 cases, each using the 6 currently employed urographic media for comparison. These included Hypaque (50 per cent), Renografin (76 per cent), Urokon (70 per cent), Miokon (50 per cent), Neo-Iopax (50 per cent), and Diodrast (50 per cent). This, of course, is too small a series for an accurate statistical study, but is adequate for a clinical evaluation of the quality of the urograms.

Evaluation of Films

The results of the study are shown in TABLES 1 and 2. It seems to us that rather extravagant claims have been made in the literature as to the percentage of diagnostic films resulting from intravenous urography. This is often reported to be as high as 94 per cent, which is certainly too high. Many films, from causes not actually ascribable to the medium itself, fail to show adequate filling of the pelves and ureters, so that the studies must be reinforced by retro-

TABLE 1

RESULTS OF STUDY MADE WITH VARIOUS MEDIA

Medium	Percentages of diagnostic films			
	Poor	Fair	Good	Excellent
Hypaque	32	12	8	48
Urokon	24	34	28	14
Miokon	28	30	34	8
Renografin	36	26	24	14
Neo-Iopax	40	24	20	16
Diodrast	44	20	20	8

TABLE 2

RESULTS OF STUDY MADE WITH VARIOUS MEDIA

Medium	Percentages of diagnostic films	
	Fair to excellent	Good to excellent
Hypaque	68	56
Urokon	76	42
Miokon	72	42
Renografin	64	38
Neo-Iopax	60	36
Diodrast	56	28

grade films. This is not infrequently the case where there has been a renal hematuria or where, for other reasons, a renal neoplasm is suspected.

It has been our practice in this study to set very rigid criteria of excellence. We gave a "good" rating only to superior films and an "excellent" only to films of practically retrograde pyelogram quality.

Statistics can be very misleading, depending on their interpretation. If the fair, good, and excellent are included in the diagnostic category, we arrive at results entirely different from those when only the good and excellent films are included. The latter procedure seems to be the preferable one, for it indicates the medium that helps us to make the diagnosis in the greatest number of cases (TABLES 1 and 2).

It is difficult to evaluate the quality of the films, because many factors are involved besides the radiopaque medium—preparation of the patient, his weight, the state of his fluid and electrolyte balance, and the quality of the X-ray technique. Further, the human factors involved in evaluation of the films, that is, the examiner's standards of excellence, are important. The latter may also change as succeeding films are read. To avoid bias, it is also essential that the examiner of the films should not know, at the time of the evaluation, which urographic medium was employed.

Renografin

Previous reports seemed to indicate that Renografin gave slightly better opacification and caused fewer reactions than Hypaque; in short, that it was a slightly better medium for intravenous urography (Lentino *et al.*, 1956). Actually, these media are similar. Hypaque is a 50 per cent solution of the diatrizoate of sodium, while Renografin is a 76 per cent solution of a mixture of the diatrizoate of sodium and methylglucamine salts of diatrizoate. The iodine concentration of Renografin is greater than that of Hypaque. Renografin, however, is more viscid and, therefore, more difficult to inject through the ordinary 21- or 20-gauge needle. It must be heated to body temperature before use to render it less viscid, and it tends to adhere to syringes, causing them to stick.

The greater viscosity is cited as an advantage because, presumably, it prevents too rapid injection. We found this viscosity to be a distinct disadvantage. The difficulty of forcing the medium through the needle necessitates greater syringe pressure, it is tiring to the operator, and leads to poorer control, so that the needle often becomes dislodged before the injection has been completed. Because of this high viscosity the solution has been diluted to 60 per cent by some (Orr *et al.*, 1956). If this is done, and 20 cc. of the medium is injected as recommended, the total amount of iodine is less than when 30 cc. of Hypaque is used.

We had no reactions, not even minor ones, with Renografin. However, we achieved only 38 per cent diagnostic films as against 56 per cent with Hypaque. Also, for some unexplained reason, the pyelographic shadows seemed to have less clarity and distinctness than those obtained with Hypaque.

Miokon

In the 50 cases where this medium was used we encountered nausea and a gagging sensation in 12; in several the reactions were severe. In this short series it was evident that Miokon is far more toxic than Hypaque. The quality of the urograms was comparable with those made with Urokon (42 per cent diagnostic films).

Actually, further studies are necessary to determine the true relative toxicity of Miokon and Renografin as compared with other media. Four deaths have occurred with Miokon and 1 with Renografin. Miokon and Renografin are fairly new compounds and are, perhaps, at the same relative stage of use as Urokon was in 1952, when only 1 death was reported as related to its use (Pendergrass *et al.*, 1958).

Before this study it had been our impression that Urokon possibly gave better urograms than Hypaque, and that the advantage of the latter lay in its lower toxicity. Actually, the films made with Hypaque (56 per cent diagnostic) were superior to those made with Urokon (42 per cent diagnostic).

Summary and Conclusions

As a result of this comparative study and our experience with 7144 cases, it is our opinion that Hypaque is, by far, the best medium now available for intravenous urography. It gives the best urograms (56 per cent diagnostic films and causes far fewer unpleasant effects and reactions than previously employed media, with the sole possible exception of Renografin. However, the latter medium, when employed as a 76 per cent solution, is so viscid that it is difficult to inject. The quality of the films we obtained with Renografin is inferior (38 per cent diagnostic). Further experience with Renografin is necessary before it can be stated definitely that it is less toxic than Hypaque.

Urokon is definitely inferior to Hypaque as far as the quality of the urograms is concerned (42 per cent diagnostic films). It is very toxic, and an appreciable number of fatalities have occurred as a result of its use.

Miokon provides urograms (42 per cent diagnostic films) that compare favorably with those obtained with Urokon (42 per cent diagnostic films). Its toxicity, although apparently less than that of Urokon, is still sufficiently great to be disturbing.

The urograms obtained with Neo-Iopax (36 per cent diagnostic films) are inferior to those obtained with Urokon and Miokon. The arm pain and the phlebitis that so often occur following injection of this medium are very objectionable features.

Diodrast gives the poorest urograms of all (28 per cent diagnostic films). It is, in addition, a very toxic medium.

Although Hypaque seems to be well tolerated by most patients and, although the incidence and severity of reactions were relatively low, we did encounter, in 7144 cases, 2 severe reactions, 1 of which ended with a fatality.

Deaths have occurred with all the commonly used intravenous urographic media. It will be possible to determine the comparative toxicity of the various media only after accurate statistics as to toxicity and fatalities become available from large series (in the millions) of examinations made with each. To achieve this end the dedicated cooperation of roentgenologists, urologists, and the manufacturers of the media in reporting toxicity and fatal reactions will be necessary.

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DIPROTRIZOATE SODIUM

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Department of Radiology, Massachusetts General Hospital, Boston, Mass.

Since the advent of the triiodobenzoic acid derivatives for excretory urography, their clinical use in the United States has evolved principally toward two compounds that are closely related chemically and physiologically. These agents are diprotrizoate (3,5-dipropionylamino-2,4,6-triiodobenzoic acid) and diatrizoate (3,5-diacetylamino-2,4,6-triiodobenzoic acid), which differ only in the nature of the substitution in the 3,5 positions on the benzene ring. Both compounds are identical except for the R groups shown in FIGURE 1.

In essence, a clinical comparative study of these compounds would attempt to measure the physiological influence of a methylene group ($-CH_2-$) in the chain. With the availability of diprotrizoate, several institutions undertook a comparative evaluation of this new agent with diatrizoate, which was already in use. A number of these studies have been reported[1-6] and, in this article, a somewhat different method of comparison is presented, together with results obtained.

In each instance, 30 cc. of a 50 per cent concentration of a sodium salt was injected intravenously into adult patients. As the diprotrizoate, Miokon* with 57 per cent iodine by weight was used; as the diatrizoate, Hypaque† with a 60 per cent iodine content was used. Each material was used during alternate weeks on all routine cases without selection as they appeared for examination in the radiology department of a general hospital.

Each patient was questioned before the examination about any possible allergies or previous reactions to urographic examinations. If any pertinent information was elicited, the doctor was called and the case further evaluated. If indicated, a test dose of the medium was given and the patient observed for reactions. Each medium was injected intravenously by the technician unless there was difficulty with the venopuncture or if the patient's history or the test dose warranted the closer supervision and administration by a physician. The average time of injection was 2 to 3 min. Evaluation covered the incidence of major and minor reactions during and after injection of the agents. The patients were watched carefully, and any significant response was recorded, as were spontaneously offered significant subjective symptoms. A doctor was immediately called for any disturbing reactions or complaints by the patient. TABLES 1 and 2 summarize the findings.

In addition to the reactions shown in TABLES 1 and 2, diprotrizoate produced 1 case each of coughing, chest pain, dizziness, generalized itching, a distressing bitter taste, and an itching nose, while diatrizoate gave 1 case each of sneezing, perspiration and pallor, abdominal distress, pain in the left abdomen, itching nose, and headache.

Of the 1329 cases studied for reactions, 1135 unselected urographs were avail-

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* Mallinckrodt Chemical Works, St. Louis, Mo.

† Winthrop Laboratories, New York, N. Y.

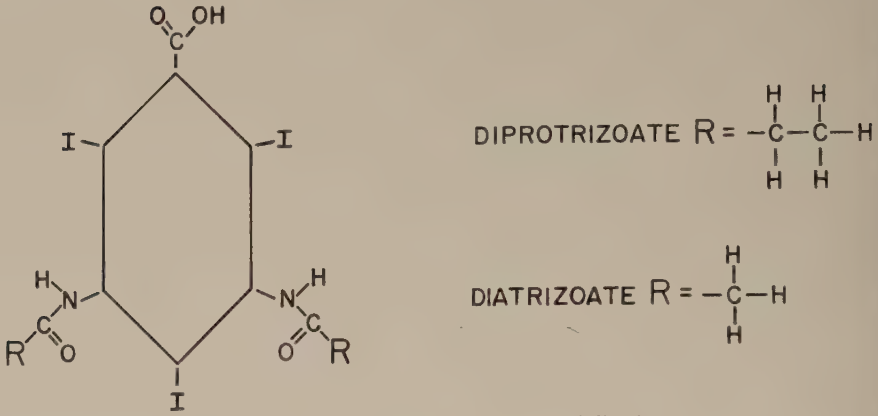

Figure 1. Structures of diprotrizoate and diatrizoate.

Table 1
Incidence of Reactions

	Diprotrizoate	Diatrizoate
Number of patients studied	647	682
Patients experiencing one or more reactions	60	68
Patient reaction rate	9.3*	10.0*
Total reactions recorded	87	82
Reaction frequency	13.4*	12.0*

* Percentages.

Table 2
Frequency of Various Types of Reactions

Type of reaction	Diprotrizoate		Diatrizoate	
	No.	Percentages	No.	Percentages
Nausea alone	30	4.6	40	5.9
Vomiting	9	1.4	11	1.6
Feeling of warmth	16	2.5	17	2.5
Flushing	9	1.4	0	0
Urticaria	7	1.1	3	0.4
Arm pain	6	0.9	5	0.7
Shortness of breath	2	0.3	0	0
Weakness	2	0.3	0	0

Table 3
Distribution of Patients by Physique

Patient physique	Diprotrizoate		Diatrizoate	
	No.	Percentages	No.	Percentages
Heavy	134	24.0	125	22.0
Medium	293	52.0	311	54.0
Thin	131	24.0	141	24.0

able for evaluation of the diagnostic quality of the examination, 558 in the diprotrizoate group and 577 in the diatrizoate group.

For purely physical reasons, visualization of a contrast medium in the urinary tract is influenced by the size of the body through which the X-rays pass and, therefore, the patient's physique was estimated and recorded by the technician. The technician is competent in making this determination, since the patient's size must be taken into consideration for the production of a satisfactory radiograph. A comparable distribution of heavy, medium, and thin patients was found in the diprotrizoate and diatrizoate groups, as shown in TABLE 3.

TABLE 4

DISTRIBUTION OF QUALITY OF PREPARATION

Quality of preparation	Diprotrizoate		Diatrizoate	
	No.	Percentages	No.	Percentages
Good	217	39.0	225	39.0
Fair	287	52.0	283	49.0
Poor	54	9.0	69	12.0

TABLE 5

DIAGNOSTIC QUALITY OF THE UROGRAPHS

Quality of urographs	Diprotrizoate		Diatrizoate	
	No.	Percentages	No.	Percentages
Excellent	130	23.0	111	19.0
Very good	185	33.0	216	38.0
Good	156	28.0	157	27.0
Fair	52	9.0	62	11.0
Poor	35	7.0	31	5.0

TABLE 6

DIAGNOSTIC QUALITY OF UROGRAPHS IN RELATION TO PATIENT PHYSIQUE

Physique	Quality of urographs	Diprotrizoate		Diatrizoate	
		No.	Percentages	No.	Percentages
Heavy	Excellent	24	18.0	19	15.0
	Very good	33	24.5	41	33.0
	Good	44	33.0	37	30.0
	Fair	20	15.0	20	16.0
	Poor	13	9.5	8	6.0
Medium	Excellent	76	26.0	55	18.0
	Very good	103	35.0	127	41.0
	Good	78	27.0	81	26.0
	Fair	23	8.0	31	10.0
	Poor	13	4.0	17	5.0
Thin	Excellent	32	24.0	42	30.0
	Very good	52	40.0	44	31.0
	Good	29	22.0	39	28.0
	Fair	9	7.0	10	7.0
	Poor	9	7.0	6	4.0

Before the full dose of any contrast medium was injected, a plain film of the abdomen was obtained; this film served to demonstrate the quality of intestinal preparation for the urographic examination. Success of preparation was estimated on the basis of overlying bowel gas, fecal matter, barium, or anything that might interfere with the visualization of the contrast material in the urinary tract. There was no significant difference between the groups in the quality of preparation interpreted as good, fair, or poor (TABLE 4).

The procedure, after injection of the agent, was to obtain at least 4-, 12-, and 20-min. radiographs using the standard positions, compression of the lower abdomen whenever feasible, and the routine technical factors for film exposure. To reduce variability, 1 person evaluated all films by the blind comparison method, during which the examiner did not know the product under study

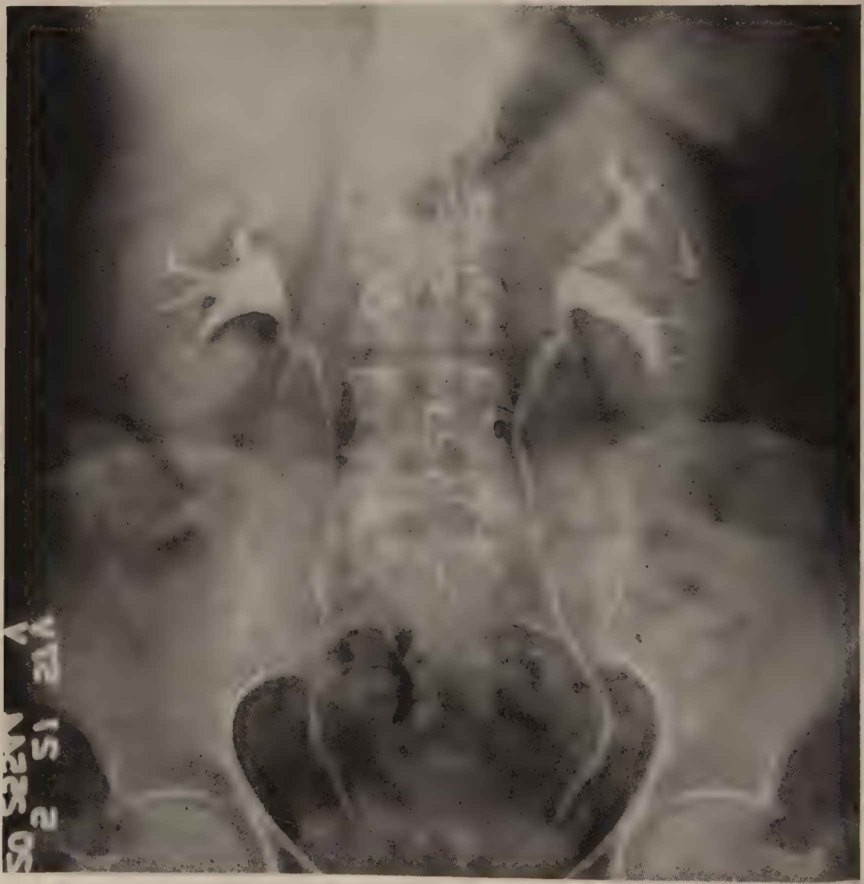

FIGURE 2. An excellent normal urograph.

until the results were finally tabulated. In determining the diagnostic quality of the urograph the examiner took into account the rapidity of appearance of the contrast material, its density, and the degree of visualization of all parts of the urinary tract. The quality of the examination was recorded as excellent, very good, good, fair, or poor. TABLE 5 shows the distribution of the diagnostic quality of the urographs.

When the results were being computed it was realized that inherent in the method was a check on the validity of the evaluation of the diagnostic quality of the urographs. As stated previously, visualization of the contrast medium in the urinary tract is influenced, for purely physical reasons, by the size of the body through which the X rays pass. If the number of urographs was sufficiently large, a correlation of diagnostic quality with patient physique would show fewer of the best urographs in the heavy patients and fewer of the poor urographs in the thin patients. TABLE 6 shows that this test of our method indicates a significant degree of reliability.

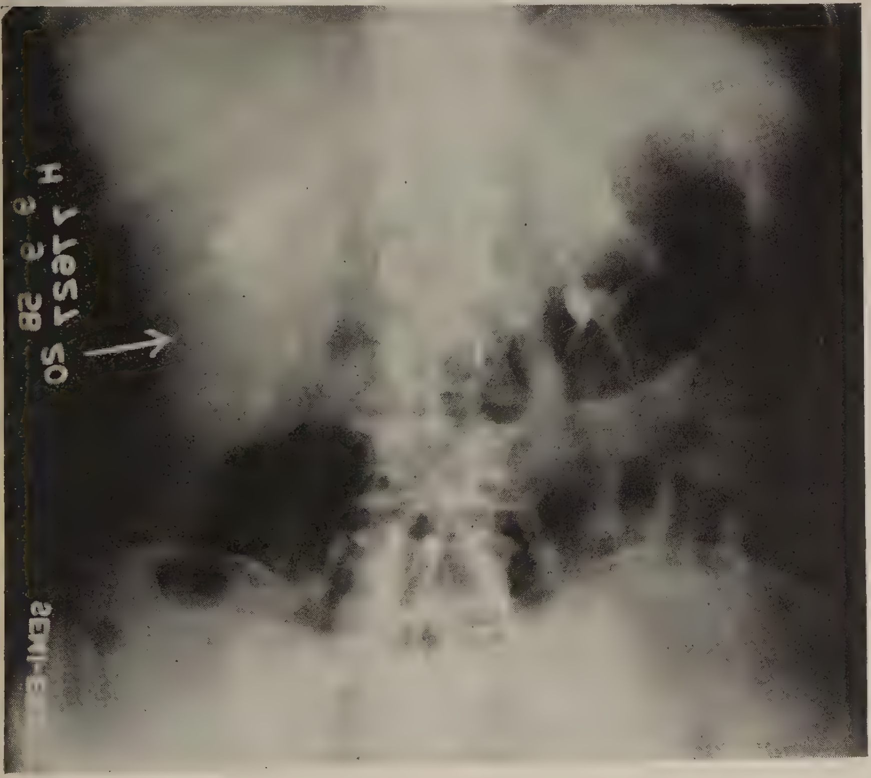

FIGURE 3. Renal cell carcinoma of the right kidney spreading and distorting the middle and lower calyces and causing dilatation of the upper calyces.

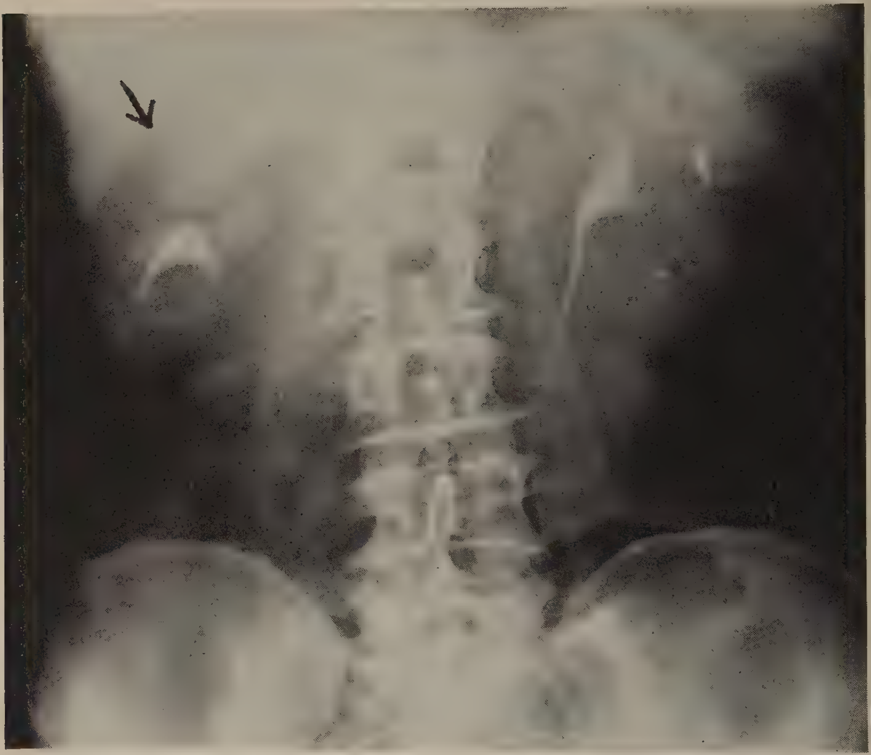

Figure 4. Carcinoma of the upper pole of the right kidney amputating the upper and depressing the middle calyces.

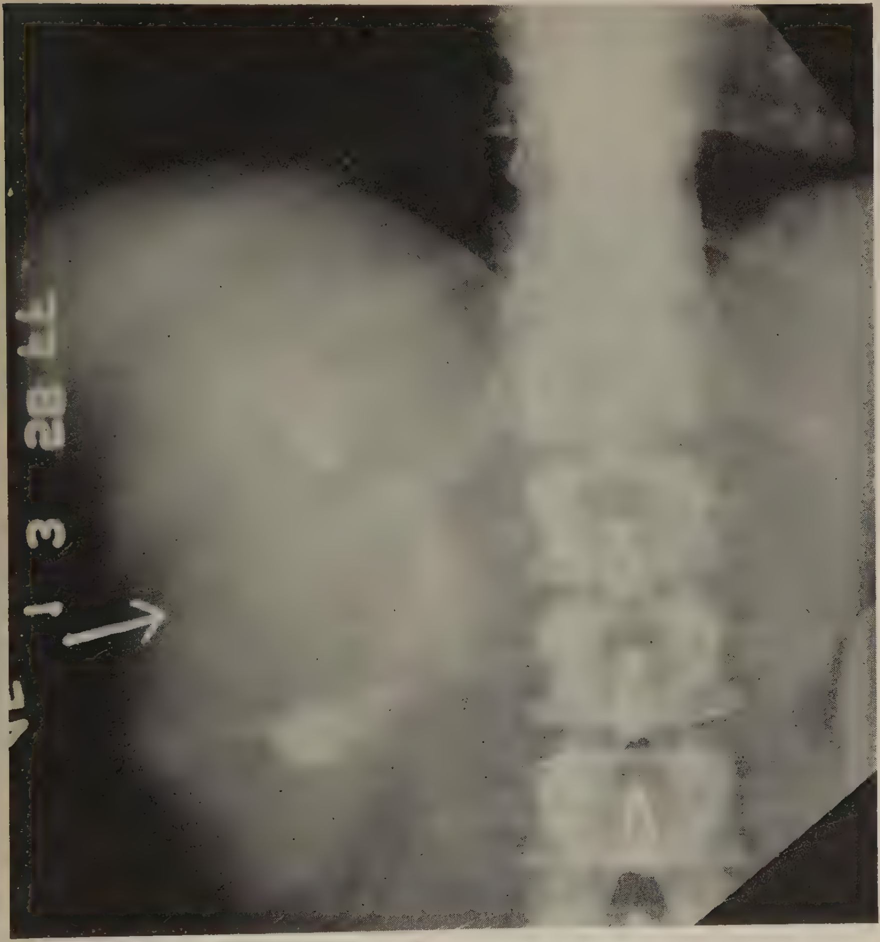

FIGURE 5. Renal cell carcinoma of the right kidney obliterating the middle, and dilating and distorting the upper and lower calyces.

The conclusions drawn from this study are that diprotrizoate is an extremely satisfactory agent for diagnostic excretory urography and that it compares favorably with diatrizoate. Diprotrizoate is one of the best agents for visualization of the normal and abnormal anatomy and physiology of the urinary tract (FIGURES 2 to 14). In this series, diprotrizoate produced slightly less nausea and vomiting, but induced more flushing and urticaria than diatrizoate. Diprotrizoate gave slightly more excellent urographs, but the percentage of good-to-excellent urographs was the same in both groups. Statistically there is no significant difference between diprotrizoate sodium and diatrizoate sodium in the incidence of reactions or the diagnostic quality of the urographs.

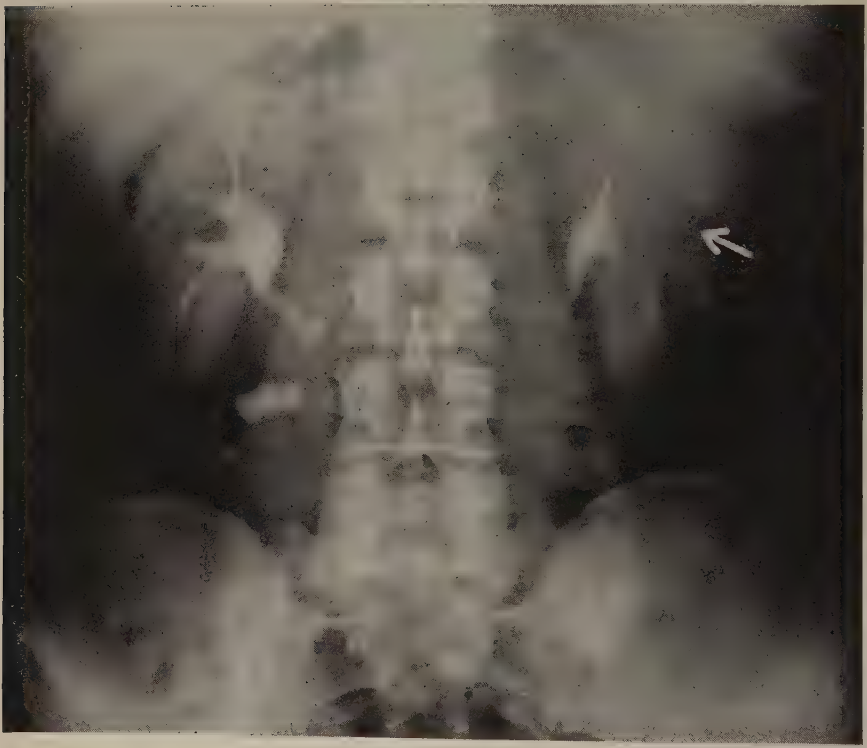

FIGURE 6. Cyst of left kidney distorting the middle and spreading the upper and lower calyces.

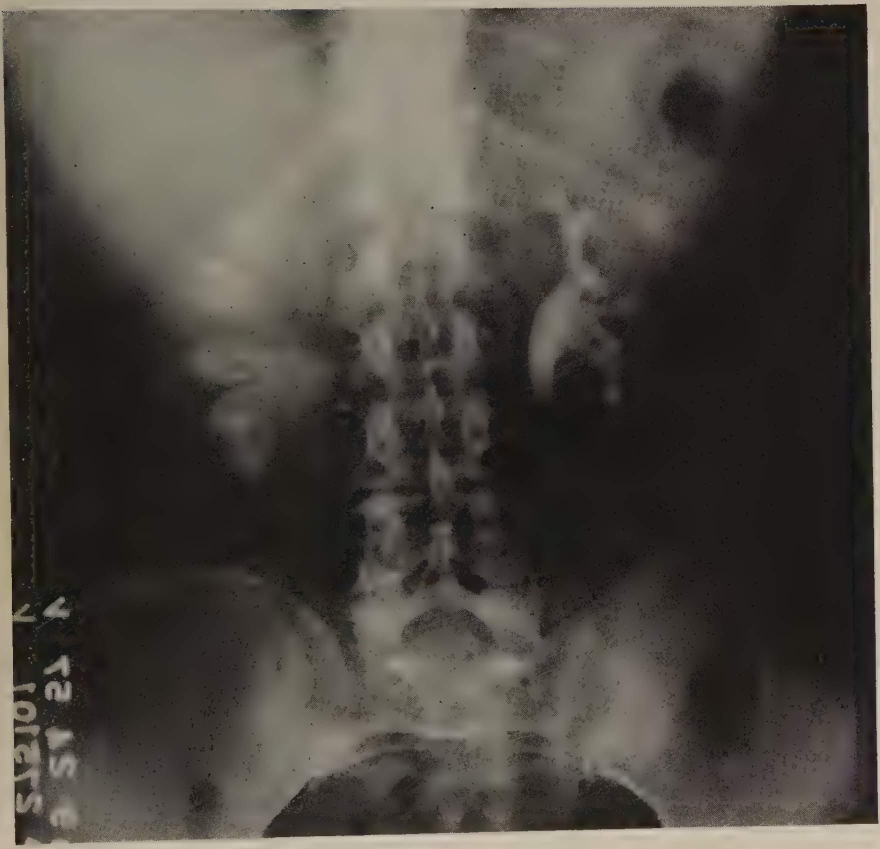

FIGURE 7. Diabetic patient with a right pyelonephritis and hydronephrosis secondary to obstruction by ureteritis cystica.

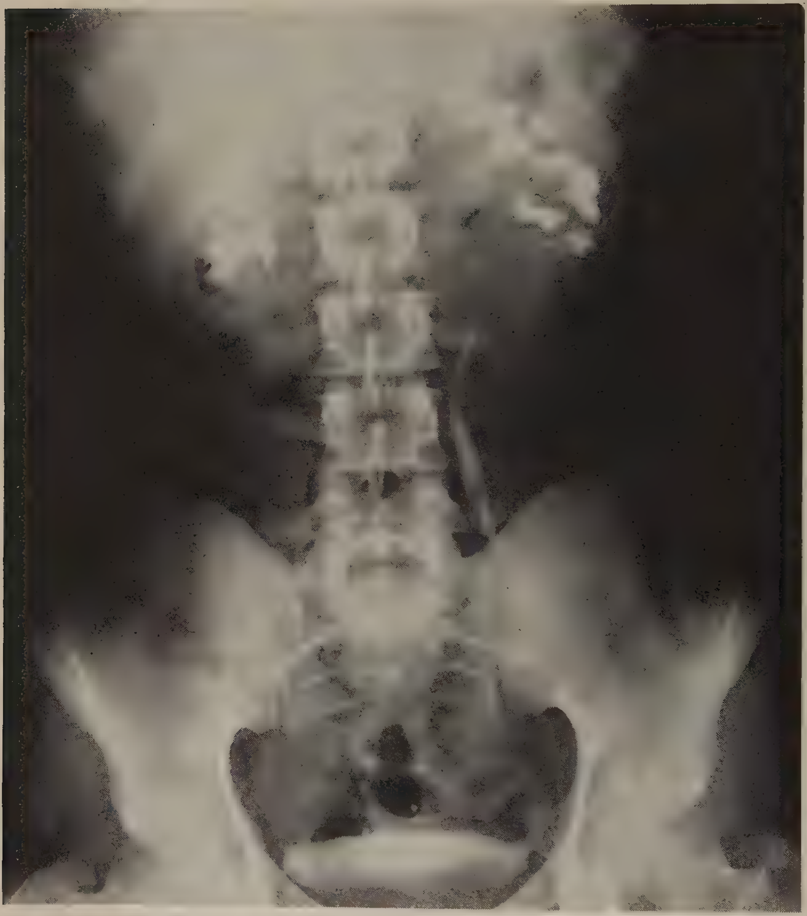

FIGURE 8. Bilateral pyelonephritis with blunted calyces and a small right kidney.

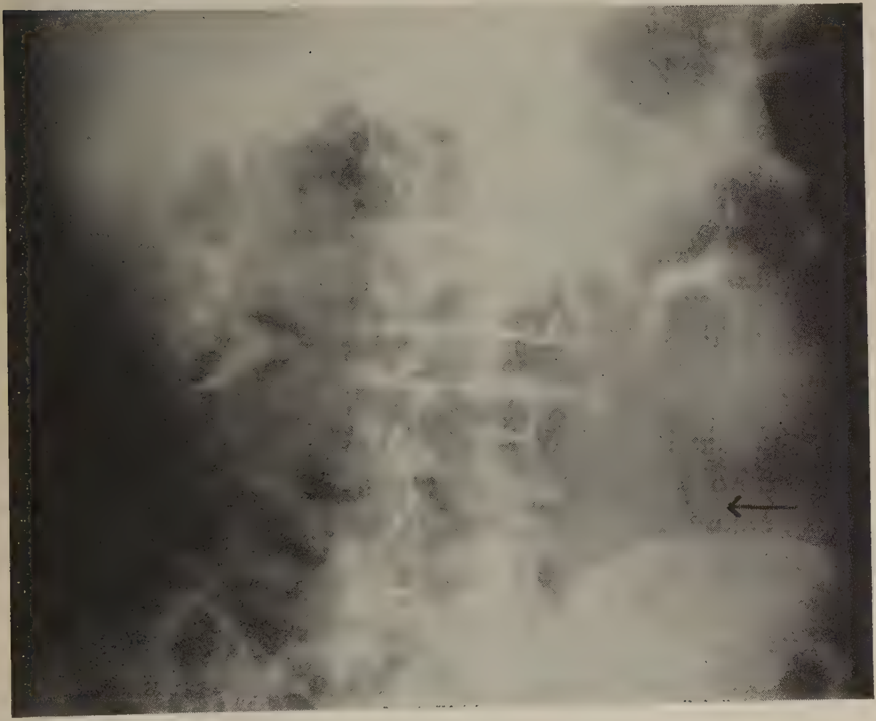

Figure 9. Lateral displacement of left ureter by an abdominal aortic aneurysm.

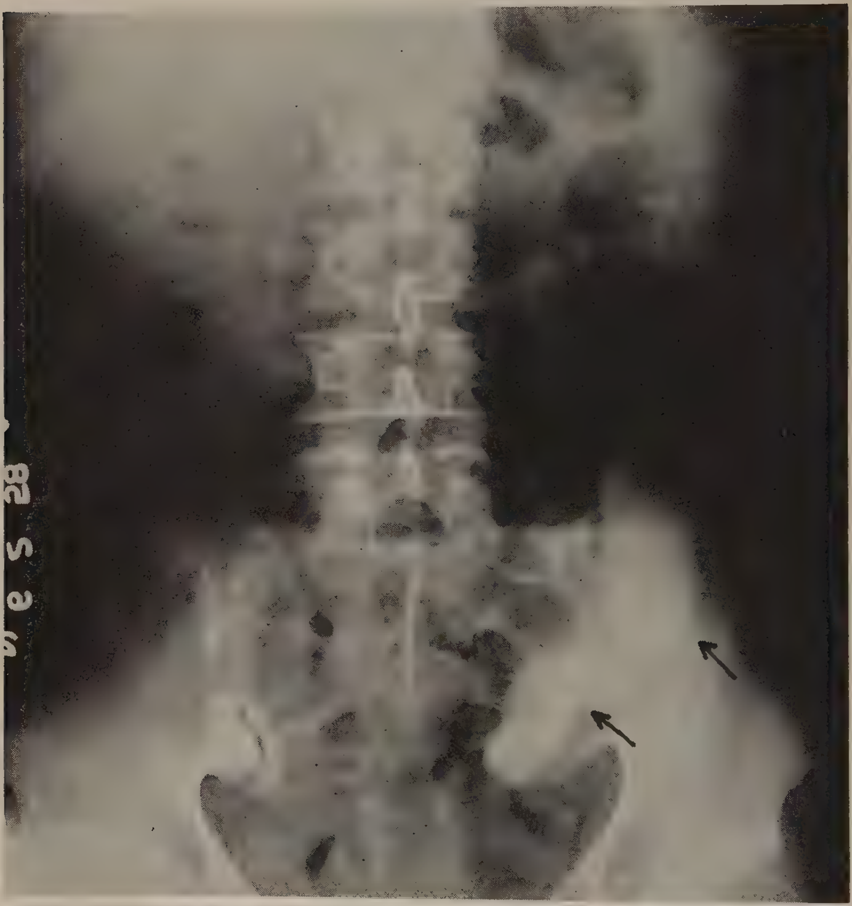

FIGURE 10. Left hydroureter due to stricture and calculus. The patient had an elevated serum nonprotein nitrogen (NPN).

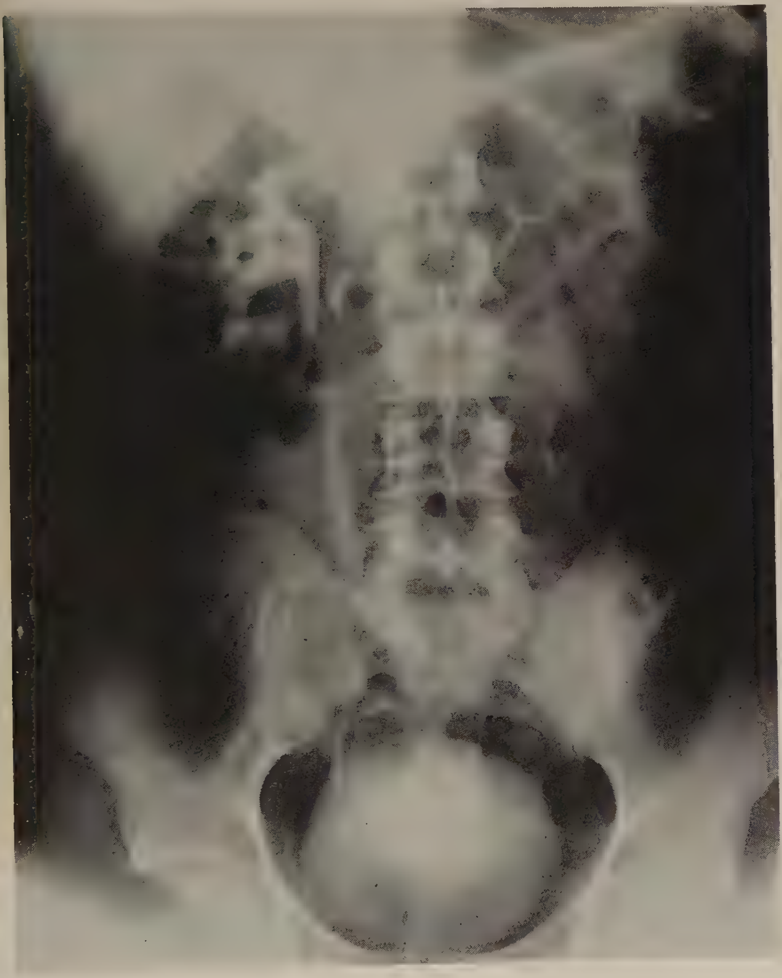

Figure 11. Right hydronephrosis and hydroureter due to an obstructing calculus at ureterovesical junction.

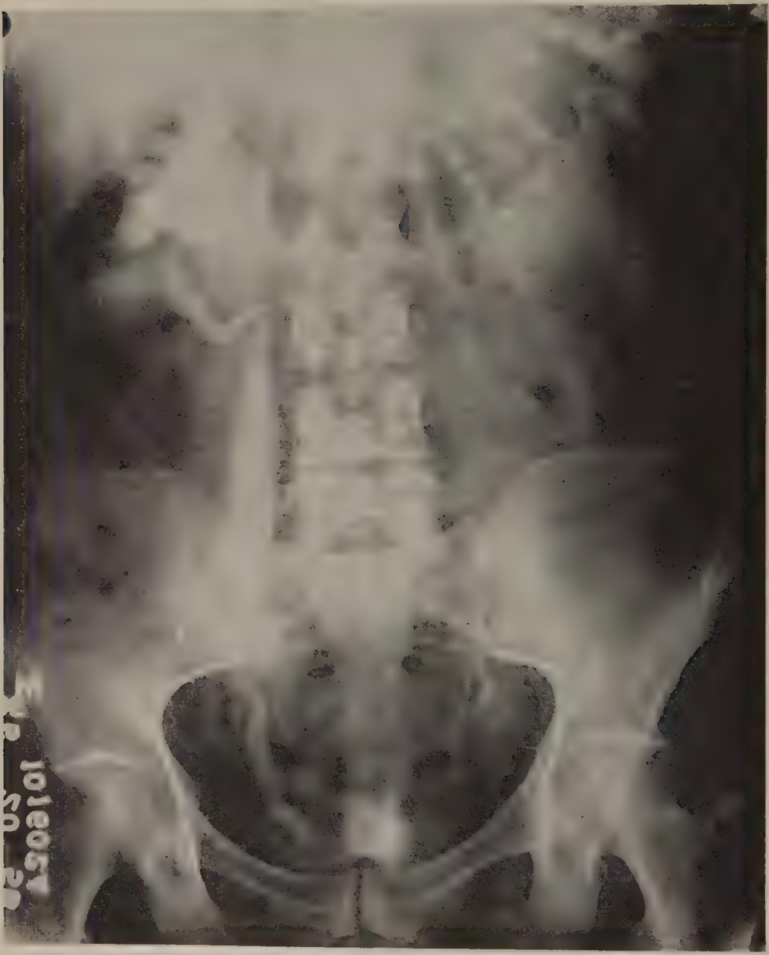

Figure 12. Right hydronephrosis and hydroureter due to obstruction from bladder carcinoma.

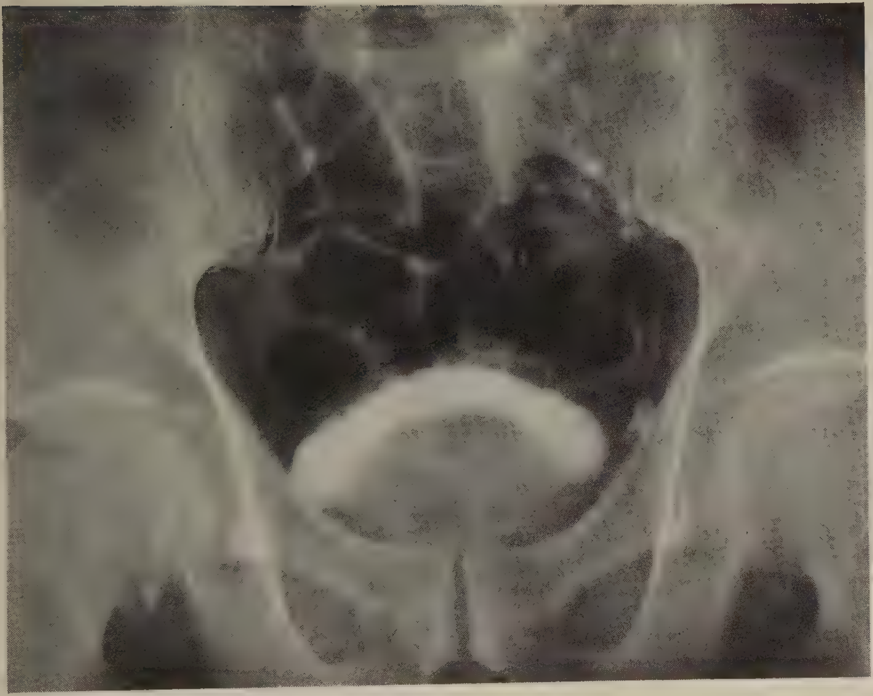

FIGURE 13. Benign prostatic hypertrophy elevating the floor of the bladder.

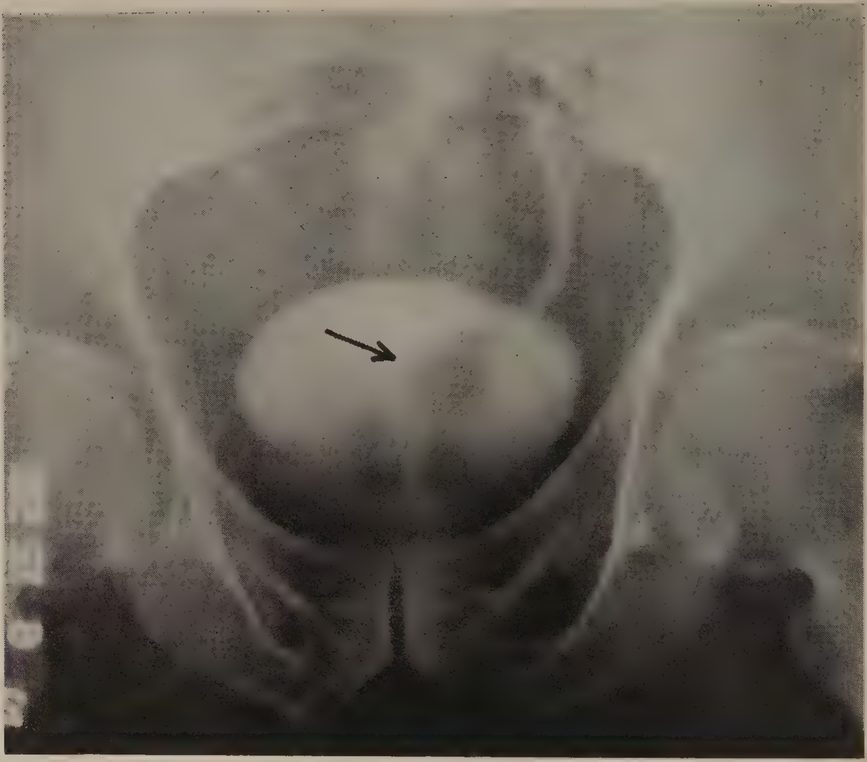

FIGURE 14. Filling defect from papillary carcinoma of the bladder.

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THIXOKON, A NEW URETHROGRAPHIC AGENT

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Daytona Beach, Fla.

The great majority of urologic problems are those that originate in disease of the lower urinary tract distal to the vesical neck. In other words, the most common urologic diseases are those of the urethra and paraurethral structures. Since this is true, it is only proper that there should be an interest in and a wide use of urethrography.

Urethrography as a technique for study is not new. For many years various researchers have made an effort to study their patients by this method and, until recently, most have been frustrated by not having a satisfactory contrast medium for the procedure. Emulsions of silver salts; suspensions of barium, bismuth, and thorium; solutions of sodium and potassium iodides and bromides; iodized oils; intravenous urographic media; and even air have been used at one time or another as cystourethrographic media, and all have obvious disadvantages. To be satisfactory simply from the diagnostic point of view, any urethrographic medium must have enough viscosity to distend and fill out the urethral canal so that minute detail will be shown and so that the medium will remain in the canal long enough to enable an adequate X-ray exposure to be made. The iodized oils are the only ones among these unsatisfactory media that possess adequate viscosity, and they are not satisfactory because of the danger of oil embolism (FIGURE 1), as reported by Grossman[1] and others.[2,3] Furthermore, being nonmiscible with urine, they do not outline the bladder base well, may produce foreign-body reactions when retained, and may be retained in the bladder and within paraurethral structures for days after injection.

The ideal urethrographic medium must have adequate radiopacity; it must be miscible with water or urine so that minute detail will be shown, so that it can be eliminated easily from the bladder, and so that there will be no danger if it enters the vascular system; it must be sufficiently viscous to distend the urethra and to remain in position long enough for proper X-ray exposure to be made; it must be relatively innocuous on contact with the urethral mucosa, so that no distortion from painful spasm will occur and so that allergic reactions will not be a problem; it must be capable of being sterilized; and it should not be injurious to urologic instruments.

Several years ago, what was thought to be a very satisfactory urethrographic medium (Visco-Rayopake) was reported by Brodney and Robins[4] and by Richards.[5] For reasons never very clearly understood by me, its manufacture was discontinued at about the end of World War II. In view of this, the manufacturer* of a new product, called Thixokon,[6-8] and which, in my experience, meets all the criteria of the ideal urethrographic medium, deserves our gratitude.

Thixokon is a thickened, aqueous solution of the sodium salt of 3-acetamido-2,4,6-triiodobenzoic acid, an organic salt containing 65.8 per cent iodine. It

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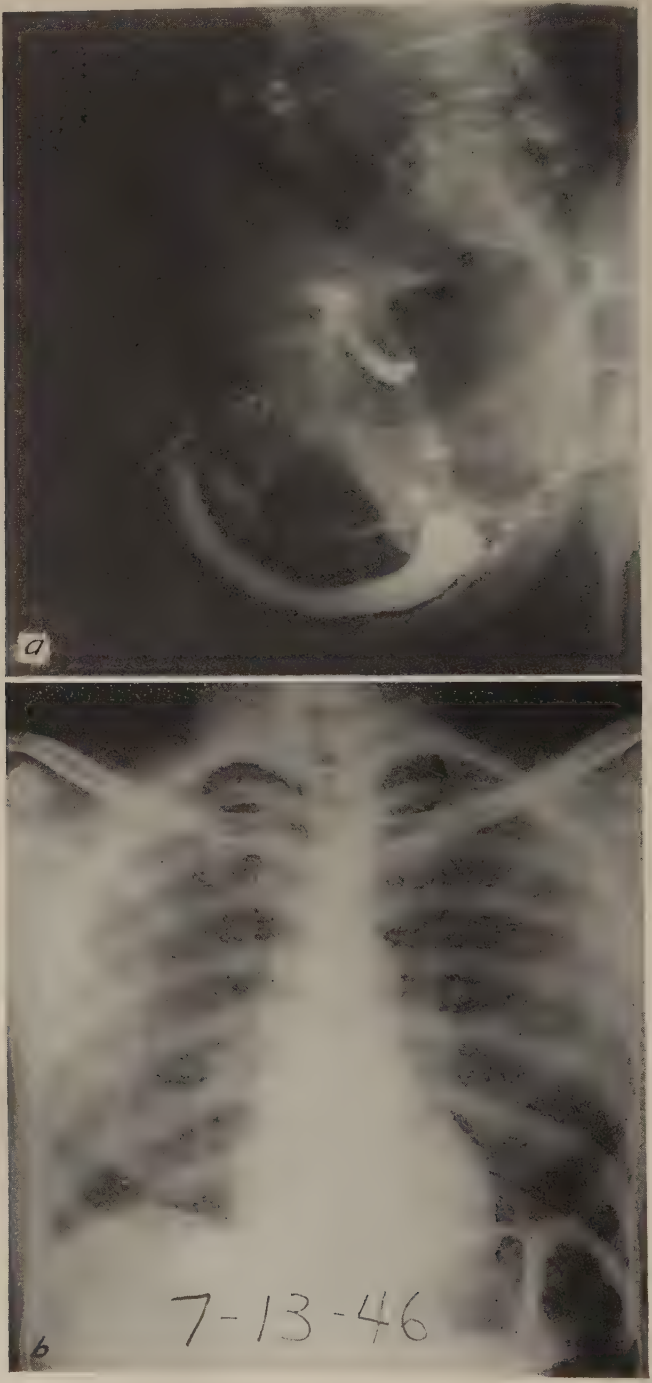
* Mallinckrodt Chemical Works, St. Louis, Mo.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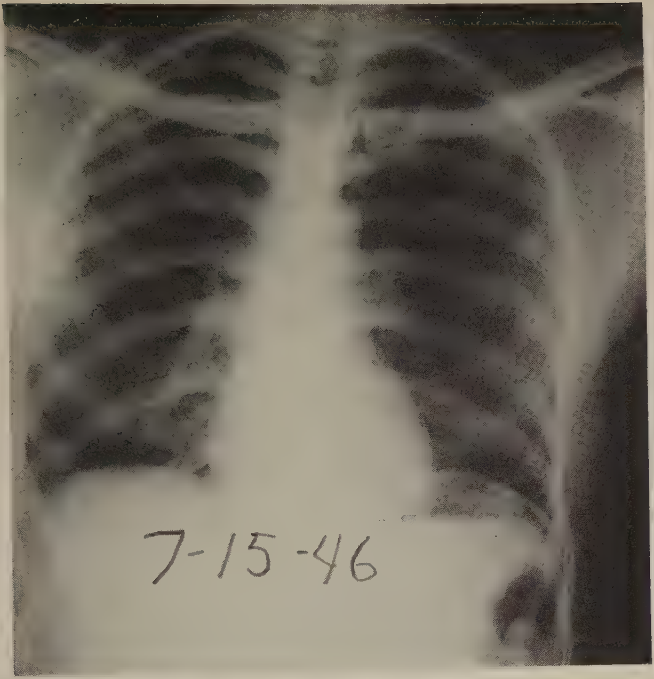


FIGURE 1. (*a*) Extravasation of contrast medium in an individual with a severe stricture of the bulbous urethra. The stricture is obscured by the contrast medium in the corpus spongiosum. Note the medium in the dorsal vein of the penis and in the pudendal veins. The use of iodized oils in situations such as this leads to oil embolization in the lungs (*b*) which, characteristically, is a finely granular change due to homogeneously dispersed tiny globules of the oil. This change can be recognized more readily by comparison with (*c*), a film of the same patient 2 days later when the condition had cleared.

is thickened with Amioca, a unique, nongelling starch consisting of nearly 100 per cent amylopectin. The term Thixokon is derived appropriately from the fact that it is thixotropic, which is to say, it has the property of being relatively fluid while being moved, but of being relatively more viscous as it comes to rest; this property favors excellent detail in the roentgenograms and ensures that the medium will "hold still" for adequate X-ray exposure. Thixokon is supplied in units of 40 cc., an amount that has been found to be sufficient for all male urethras.

I have used Thixokon for the past 3½ years. During this time I have made more than 500 urethrograms with this new medium. From that experience I feel justified in making the following observations. Thixokon produces roentgenograms of uniformly excellent quality. I never have had a poor film in which the fault could be attributed to the contrast medium. Since Thixokon is water-miscible and the starch is hydrolyzed readily; excellent fine detail is obtained; there need be no concern about emboli if vascular invasion occurs; and the medium is discharged readily and completely by the bladder. Although the mechanical trauma of instilling a viscous solution into pathologic urethras not uncommonly produces some bleeding, aftereffects of the diagnostic study with Thixokon have been minimal, and only 1 patient has experienced any significant trouble; this man was a sexual psychopath who had a normal urethra.

Of course, since Thixokon depends for its radiopacity on an organic iodide that also is used for intravenous urography, prudence dictates that we have the necessary means at hand for combating anaphylactic reactions that might occur in hypersensitive individuals. I am happy to be able to report that I have had no reaction of this kind with Thixokon.

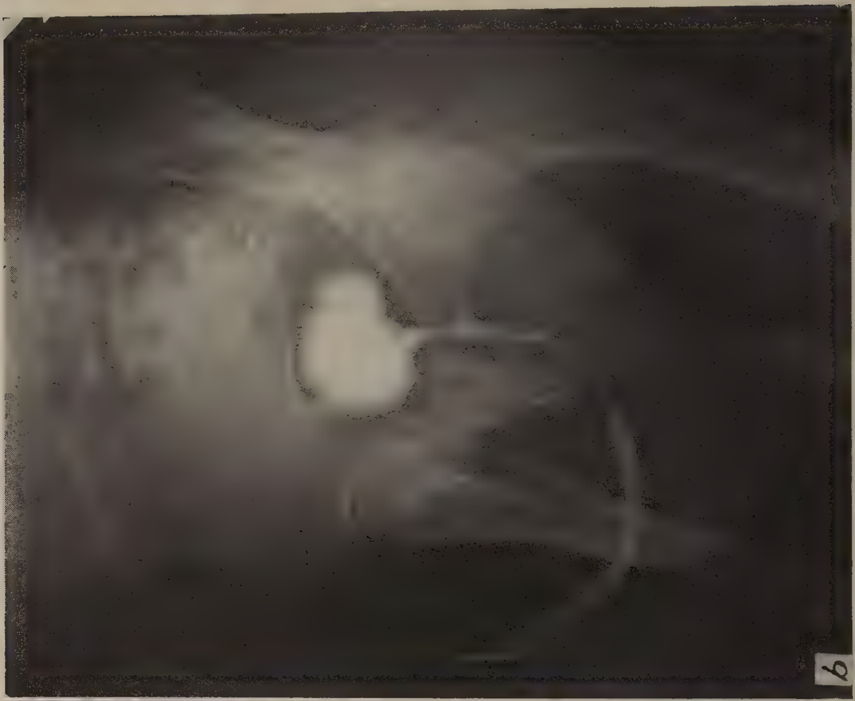
Urethrography is an exceptionally worthwhile diagnostic study that has not attained the popular use among urologists and radiologists that it deserves. Now that Thixokon is available, surely more urethrograms should and will be done.

For routine use, just one oblique film exposed during the latter part of the instillation has been of tremendous value to me. The "bird's-eye view" that one gets of the urethra is much more enlightening than the limited information available by mechanical exploration or probing. Many times, when urethral disease precludes the initial passage of urethroscopic instruments, urethrography may be the only means by which one can get a true and comprehensive idea of the condition. A routine urethrogram done prior to prostatic surgery can help avoid the embarrassment of having difficulty passing the resectoscope because of strictures or false passages not known to be present, and it can help a great deal in determining the operative approach of choice as well as any preoperative maneuvers such as dilation of strictures that may be in order; it also may be very reassuring as a record of the existence of a preoperative stricture that is troublesome postoperatively (FIGURE 2).

I do not wish to create the impression in my enthusiasm for urethrography that I consider it a panacea for all the diagnostic problems relative to the lower urinary tract. There have been a number of occasions when cystourethroscopy has shown my interpretation of the urethrogram to be faulty; however, these usually have been errors of omission, as when the urethrogram fails to show a median bar or vesical-neck contracture, and the errors almost always relate to conditions at or proximal to the vesical neck.

Most of my urethrograms are done in my office on ambulatory patients and, for this purpose, I use a Hugh Young Table equipped with a 200-mAmp. X-ray machine with a rotating anode tube. We commonly use 200 mAmp. at 80 kv., with an exposure time of 1 sec., and a 44-in. tube-to-film distance. At a 30-in. tube-to-film distance, the exposure time may be reduced by half. For smaller machines, 30 mAmp. at 85 to 90 kv., with a 3-sec. exposure at 30 in., or 75 mAmp. at 70 to 75 kv., with a 2-sec. exposure at 30 in., have been satisfactory. It should be noted that a tube-to-film distance of at least 36 in. (40 in. or more is even better), and the use of 80 kv. or higher tend to reduce the total radiation exposure of the patient and, of course, in this day when all are becoming radiation conscious, we know this is desirable. A limiting diaphragm and 3 mm. of added aluminum filtration are used routinely and are recommended. Routine urethrograms in the oblique position require a greater exposure than do routine plain roentgenograms of the abdomen. In general, if one must err

FIGURE 2. (*a*) Normal urethrogram. Note the symmetrical, funnel-shaped bladder outlet; the smootheness and symmetry of the prostatic urethra, which is only very slightly curved anteriorly; the uniform density of the contrast medium in the prostatic urethra, save for the filling defect caused by the verumontanum; the normally large bulbous urethra; and the generous-sized penile urethra. (*b*) Multiple, postgonococcal urethral strictures. (*c*) Long standing, postgonococcal urethral stricture with false passage. This patient also shows contracture of the vesical outlet from chronic prostatitis with scarring and some B.P.H. (*d*) Typical B.P.H. Note the broadening and thinning of the prostatic urethra due to lateral-lobe enlargement and the anterior angulation caused principally by enlargement of the median lobe, which extends into the bladder. (*e*) Large B.P.H. This adenoma weighed 165 gm. Note marked broadening, thinning, anterior angulation, and lengthening of the prostatic urethra. (*f*) Carcinoma of the prostate. Note the thin, gun-barrel, prostatic urethra which, in this patient, also is elongated. A similar change may be seen in patients with chronic prostatitis and stenosis of the prostatic urethra from scarring. This patient also had a urethral stricture that is obscured by extravasation of contrast medium into the corpus spongiosum.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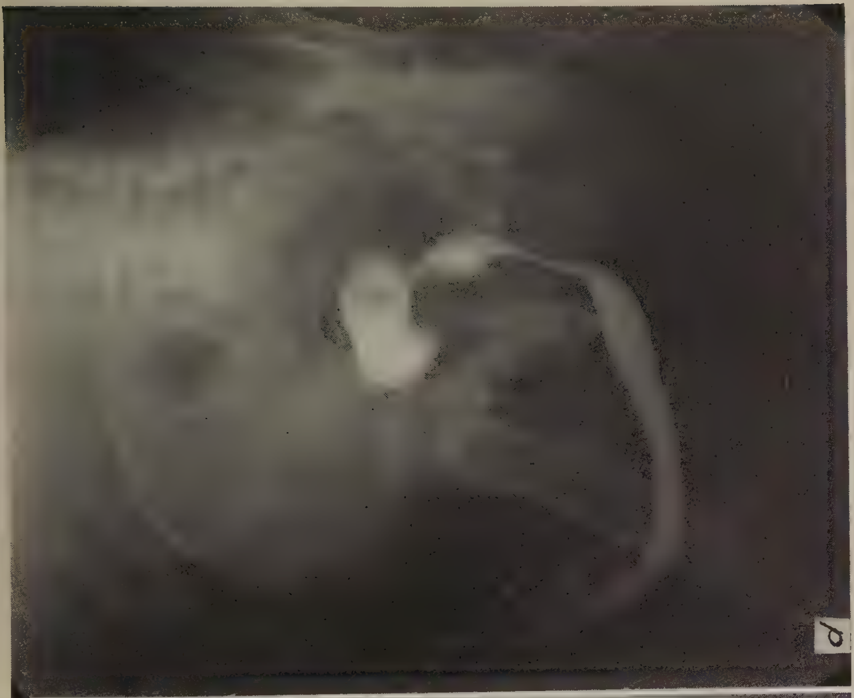
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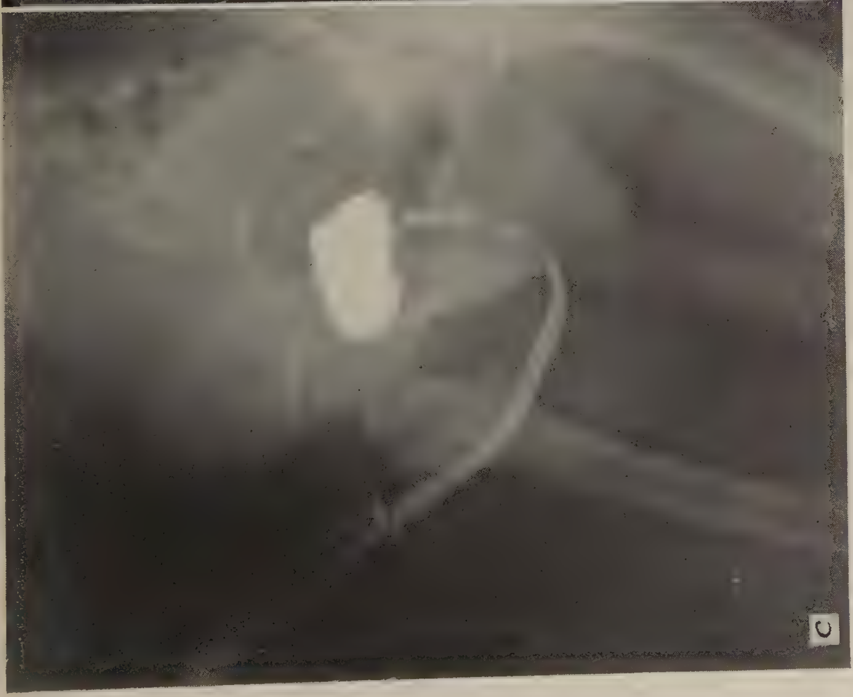
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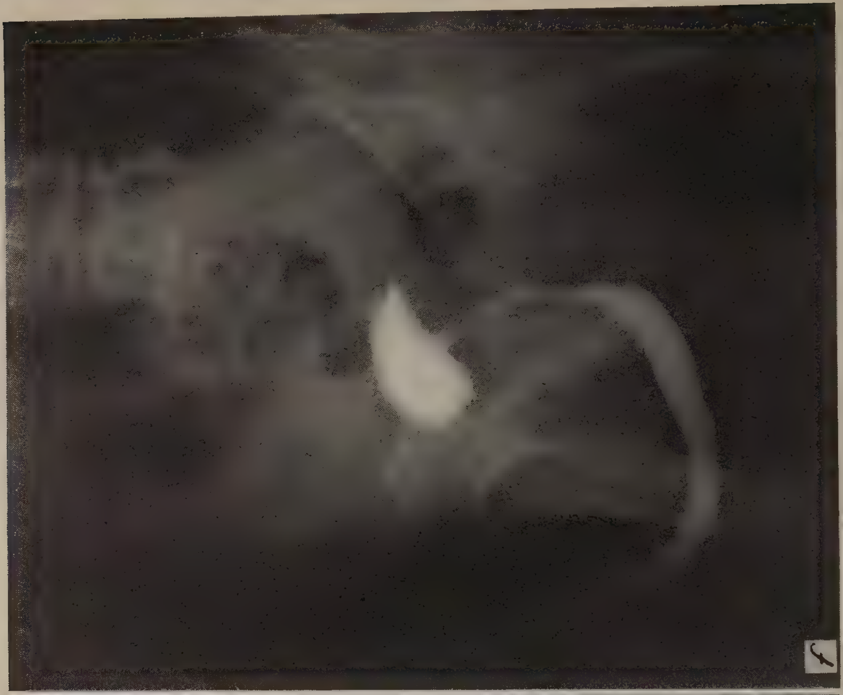

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in exposure, one should err on the side of over- rather than underexposure. Underexposure is likely to result in a film that is not of diagnostic value thus leading to another exposure. Since Thixokon has a high degree of radiopacity, it is almost impossible to "burn it out" within the usual limits of error, and films of diagnostic value can be obtained even with considerable overexposure. The use of the newer, high-speed X-ray films, of course, helps to get good exposure of the film without overexposure of the patient.

For those interested in learning more about urethrograms and their interpretation, I recommend *Radiologic Diagnosis of the Lower Urinary Tract* by Beard *et al.*[9] There are a few general points regarding the making of urethrograms that deserve emphasis. For routine urethrography, one oblique film has been of the greatest value. The patient should not be asked to hold his breath during the exposure of the X-ray film; this is likely to cause closure of the external sphincter. For the same reason, the exposure should be made during the actual instillation of the last few cubic centimeters of the Thixokon. I feel that the Brodney instrument for urethrography works very well and I use it;[10] however, any method of introduction of the contrast medium necessarily distorts or obscures the distal 2 or 3 cm. of the urethra. Complete evaluation of the urethral meatus and fossa navicularis is important and is accomplished easily by exploring these areas with a *bougie à boule* or a Thackston stricture detector[11] while the film is developing (FIGURE 3). Although occa-

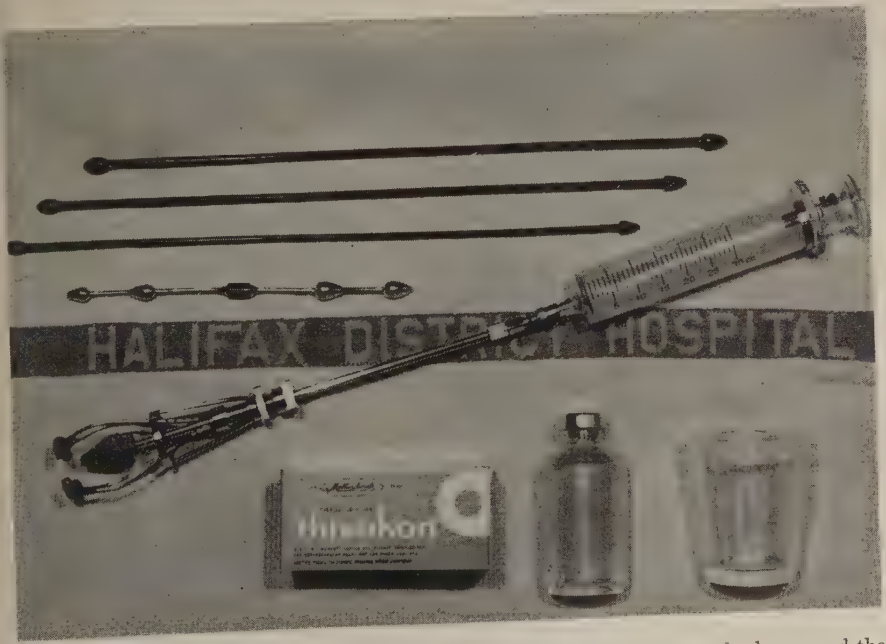

FIGURE 3. Apparatus for doing urethrograms: Thixokon, Brodney urethral gun, and the Thackston stricture detector or *bougie à boule* for exploring the urethral meatus and fossa navicularis.

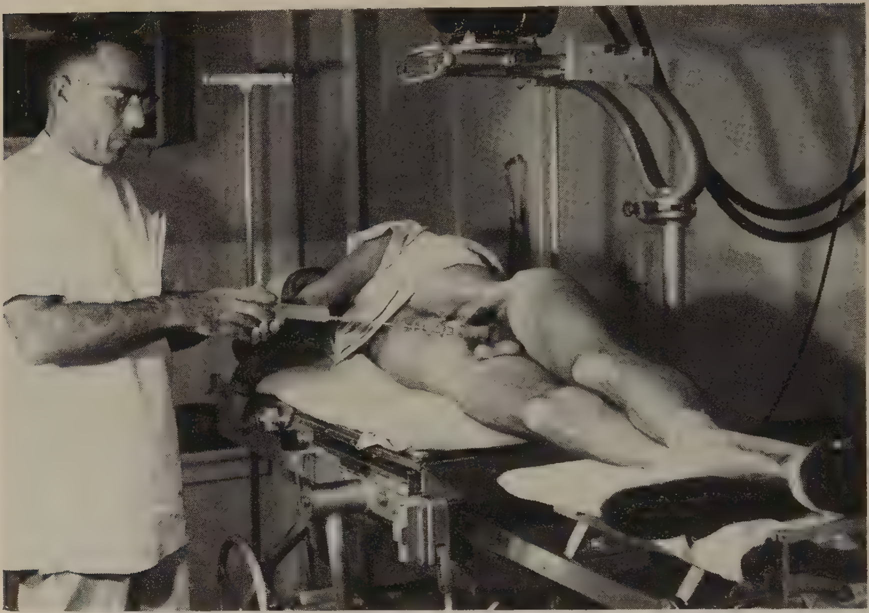

FIGURE 4. Position and method for carrying out routine urethrography.

sionally that part of the contrast medium that overflows into the bladder may provide a clue about intracystic disease, one easily can be mislead by the bladder picture. A final interpretation of bladder disease should be made only upon more appropriate studies such as cystoscopy or cystography and not upon the incidental findings in urethrography alone (FIGURE 4). Since Thixokon is water-soluble, it has been suggested that, if the patient is not permitted to void after a urethrogram, cystograms could be made with the same contrast medium dissolved in the urine. This is true, but we have found that it takes considerable time for the Thixokon, lying dormant in the bladder, to be dissolved. If there were something to stir the mixture, of course, solution would occur much more rapidly. From a practical point of view and with respect to the time consumed, the technique is not entirely satisfactory.

Patients are better informed and more curious about themselves than formerly. Many of us have found it desirable to use visual aids to improve patients' understanding of their problems. I suggest that urethrograms, properly explained, can be understood readily by the patient of average intelligence. To have his problem removed from the realm of mystery and explained with media that he can understand allays apprehension and develops confidence in himself and in his doctor.

Summary

Since the majority of urologic patients have their principal disease in the urethra or paraurethral structures, and since urethrography is a valuable diag-

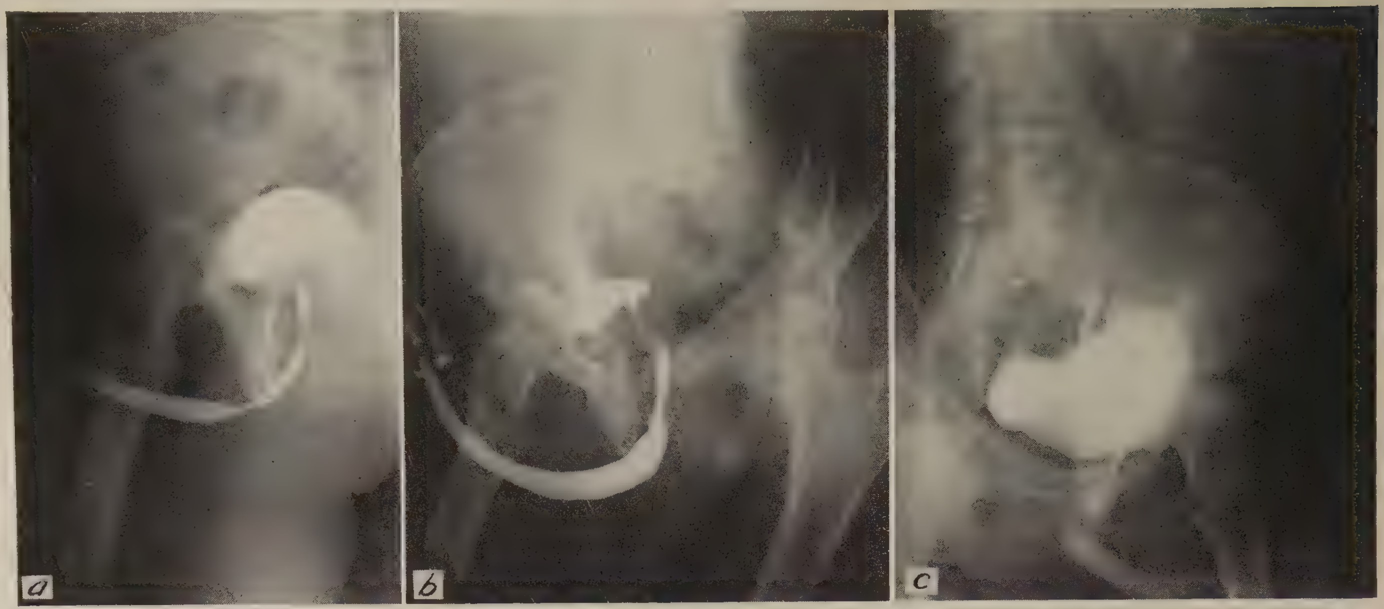

FIGURE 5. (*a*) Combined excretory cystogram and routine urethrogram, showing that the contrast medium that overflows into the bladder during urethrography is not a reliable index to the true outline of the bladder. (*b*) Diverticulum suspected on the urethrogram as a result of overflowed medium, and confirmed by (*c*) a cystogram.

nostic aid for the study of urethral and paraurethral problems, there has been a long-felt need for an ideal urethrographic medium. This need has been fulfilled very well by Thixokon. In my experience with more than 500 urethrograms done with Thixokon, this medium has been uniformly satisfactory in all respects. Certain aspects of the technique of making urethrograms and of their interpretation have been discussed, and illustrative material has been presented.

As a now completely safe, reliable, and useful diagnostic aid, urethrography deserves greater use.

Acknowledgment

I thank Earl Q. Heist for his invaluable help and W. R. Armstrong and Floyd P. Hallett of the Department of Medicinal Product Development, Mallinckrodt Chemical Works, for supplies of Thixokon and for their continued interest in this study.

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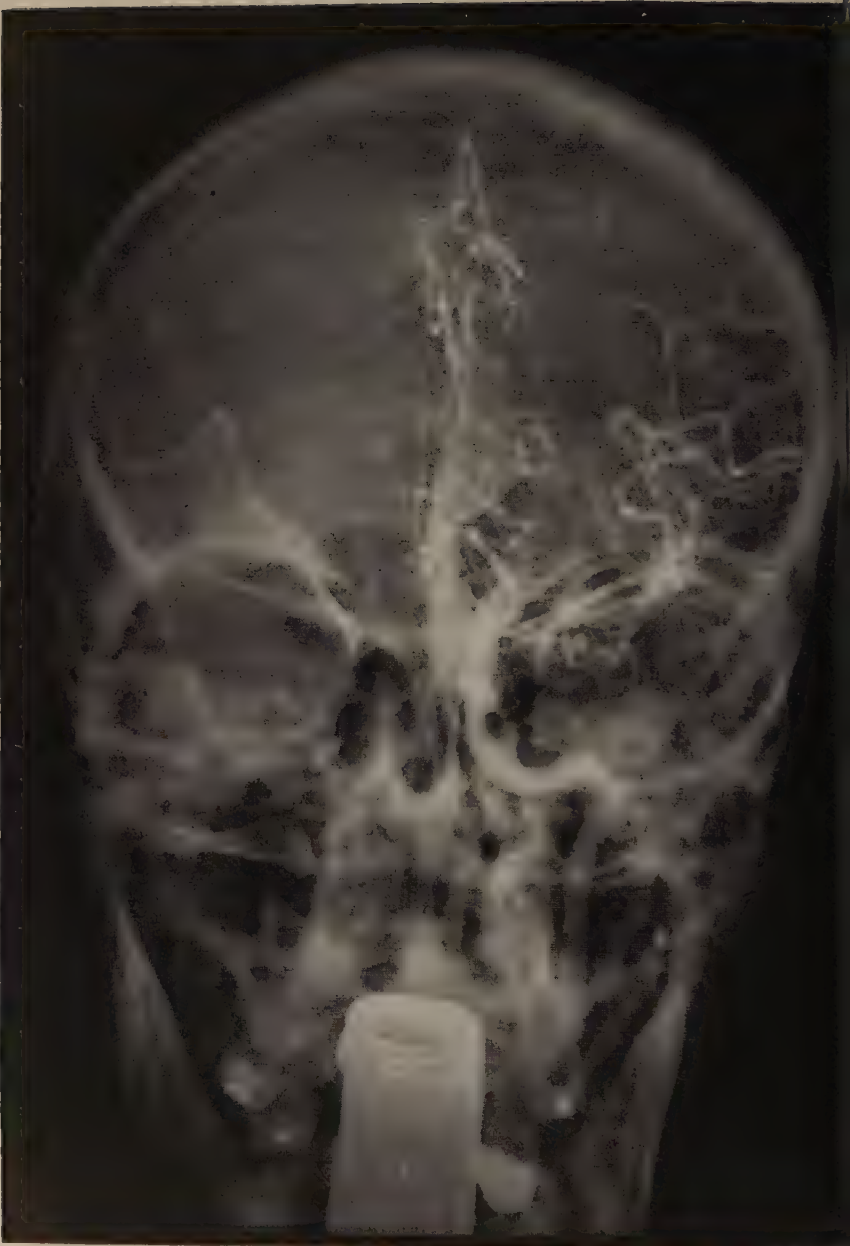

FIGURE 5. Films Nos. 1 and 2 of a series of 6. This stereoscopic pair demonstrates t
existence of a clotted aneurysm surrounded by a very rich collateral vascular circulation n

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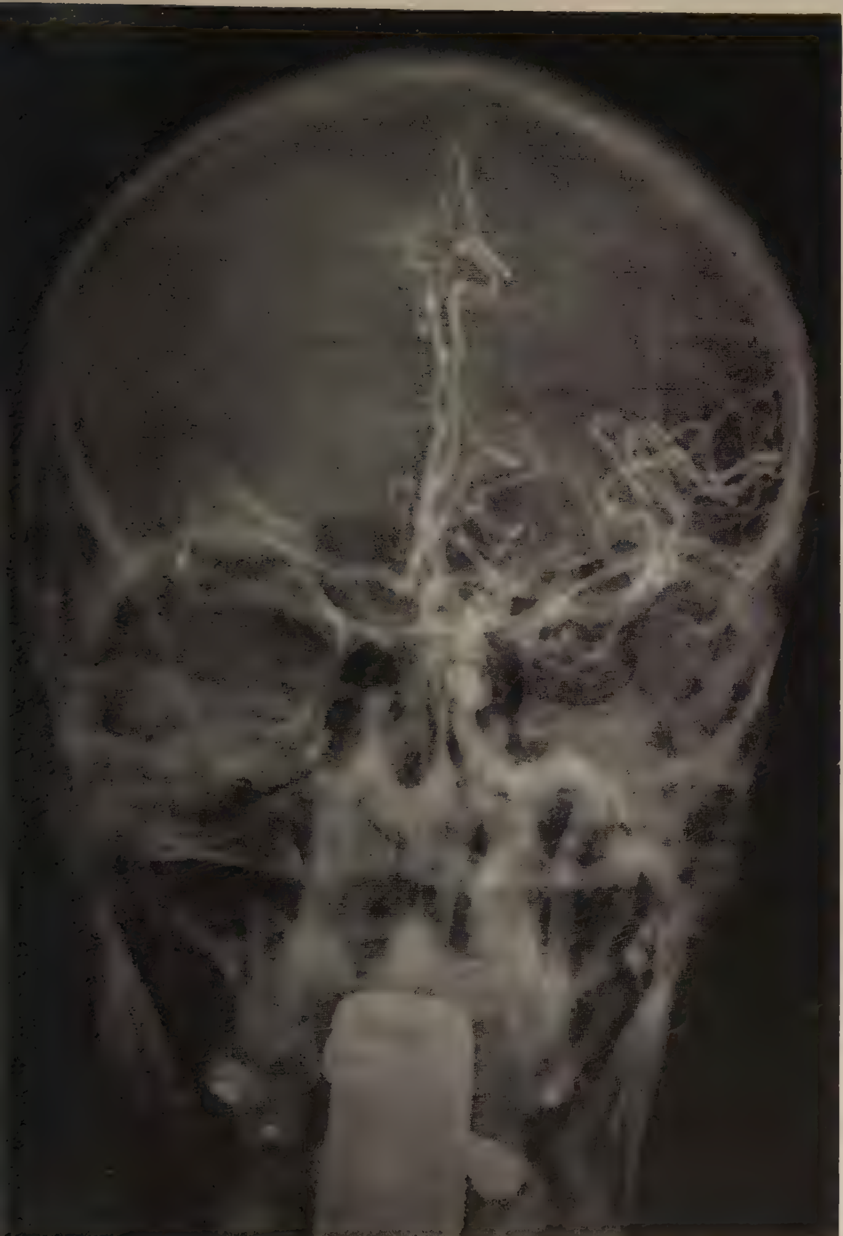

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